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par
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MAITRISE DU SURPOIDS :
INTERET DES REGIMES ET PLACE DES COMPLEMENTS ALIMENTAIRES RENFERMANT DES ACTIFS AMINCISSANTS : CAS DU THE VERT ET DU GLUCOMANANNE

WEIGHT LOSS SUPPORT:
STUDY OF OVERWEIGHT, DIETING AND DIETARY SUPPLEMENT CONTAINING SLIMMING ACTIVE INGREDIENTS: CASE OF GREEN TEA AND GLUCOMANNAN

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INTRODUCTION

Aujourd'hui dans le monde, la population en surpoids augmente régulièrement. Le corps mince et sculpté que les médias prônent depuis 40 ans est en totale contradiction avec la tendance au surpoids et à l'obésité qui se développe globalement. L'Organisation Mondiale de la Santé (l'OMS) décrit l'obésité comme étant un fléau, très visible, mais très négligé par les autorités de santé, qui menace de submerger les pays développés et en voie de développement (WHO, 2000). En effet, l'obésité est aujourd'hui reconnue comme étant la seconde cause de décès évitable, dépassée uniquement par le tabagisme.

La présence d'un régime alimentaire déséquilibré et d'un mode de vie sédentaire accroissent les apports énergétiques, tout en réduisant les dépenses, favorisant la prise de poids. Il existe d'autres facteurs influençant l'apparition de surpoids tels que la prédisposition génétique, certains médicaments, les anomalies hormonales, le psychisme etc.

Cette thèse explore le surpoids, l'adipocyte ainsi qu'une large panoplie de stratégies de perte de poids connus en France allant des régimes Weight Watchers et Dukan aux compléments alimentaires minceur avec un focus sur leurs principes actifs, notamment le thé vert et le glucomannane.

Elle a pour objectif d'aider le pharmacien à comprendre les problématiques, les besoins et les désirs des personnes en surpoids ou obèses de manière à les conseiller plus efficacement.

PARTIE 1 : SURPOIDS ET OBESITE

Le surpoids et l'obésité sont définis par l'OMS comme étant une accumulation excessive de masse graisseuse qui pourrait être délétère pour la santé. L'indice de masse corporelle (IMC) est communément utilisé afin de déterminer si une personne est en surpoids (IMC de 25-29.99) ou obèse (IMC ≥3O). Il est calculé par le poids en kilogrammes divisé par la taille au carré en mètres carrés. En Europe, environ 58% des hommes et 51% des femmes sont en surpoids.

La raison principale du développement du surpoids est une balance énergétique chroniquement positive. En d'autres termes, cela signifie qu'une personne absorbe plus d'énergie qu'elle n'en consomme sur une longue période de temps, conduisant au stockage du surplus dans le tissu adipeux. Ceci peut être dû à un excès d'apports caloriques, par exemple par une suralimentation, ou à une réduction du métabolisme basale lié, par exemple, à une fonte musculaire. D'autres facteurs influencent l'apparition de l'obésité notamment les habitudes de vie dont le manque d'activité physique et le sommeil, mais aussi les facteurs sociologiques et génétiques, la composition de la flore intestinale, ainsi que les altérations métaboliques et endocrines.

L'obésité et le surpoids peuvent mener à des complications à la fois physiques et psychologiques. Les répercussions physiques incluent les comorbidités telles que les maladies cardiovasculaires, l'hypertension, le syndrome métabolique, le diabète, les maladies inflammatoires, les troubles musculo-squelettiques, ainsi que les répercussions esthétiques telles que la cellulite (qui constitue la plainte esthétique la plus répandue chez les femmes tout IMC confondu) mais aussi la distension de la peau ou l'hypersudation. Psychologiquement, le surpoids peut mener à des répercussions telles que le sentiment de rejet, de stigmatisation, de discrimination sociale, etc. Cela peut également entrainer la perte de la confiance en soi, la non acceptation de soi-même, des troubles du comportement alimentaire ou l'isolation.

Les médias ont un rôle important à jouer dans l'émergence des répercussions psychologiques pour les individus en surpoids car ils prônent « le dicta de la minceur » et proposent souvent des méthodes de perte de poids qui sont parfois controversées.

PARTIE 2 : TISSUS ADIPEUX

Le tissu adipeux est caractérisé par la présence d'un grand nombre de cellules remplies de lipides appelés adipocytes, maintenues ensemble grâce à un réseau de fibres de collagène. Les adipocytes sont des cellules métaboliquement actives qui jouent un rôle central dans la balance énergétique du corps mais aussi un rôle endocrine et paracrine car ils secrètent de nombreux facteurs (Franchi *et al.,* 2003). Les rôles primaires de l'adipocyte consistent à isoler et protéger le corps, ainsi qu'à stocker des acides gras libres après les prises alimentaires (lipogénèse) et de les libérer (lipolyse) tout au long de la vie (Hajer *et al.*, 2008). Les adipocytes jouent également un rôle dans le métabolisme glucidique et lipidique ainsi que dans la production de cytokines et d'hormones (Bacci *et* Leibaschoff, 2006).

Le tissu adipeux peut se trouver au niveau hypodermique, viscéral ou périphérique. Chez un individu de poids moyen, 15 à 20% de son poids corporel est composé de tissu adipeux, ce qui correspond à environ 50 à 80 milliards d'adipocytes (Dubois, 2007 ; Fritsch *et* Kühnel, 2003 ; Melissopoulos *et* Levacher, 1998).

L'hypoderme est surtout composé d'adipocytes. Son épaisseur est variable : elle est fine au niveau du front et épaisse au niveau du fessier. Il y a également des différences entre l'emplacement du tissu adipeux sous-cutané chez les hommes et chez les femmes. Chez les hommes, la distribution adipeuse est généralement « au dessus de la ceinture » c'est-à-dire dans l'abdomen et les épaules, nommé « androïde ». Chez la majorité des femmes, la distribution de la masse graisseuse sous-cutanée est essentiellement « gynoïde », c'est à dire localisée « en dessous de la ceinture » au niveau des cuisses et des fesses. La distribution graisseuse androïde est souvent comparée à la forme d'une pomme alors que la distribution gynoïde à celle d'une poire (Melissopoulos *et* Levacher, 1998; Meynadier, 1980; Dubois, 2007). Ces différences de distributions sont surtout influencées par les hormones sexuelles et sont particulièrement marquées en cas de surpoids ou d'obésité.

La cellule adipeuse est une cellule sphérique dont le cytoplasme est constitué d'une vacuole remplie de triglycérides. La vacuole contenant des lipides déplace le noyau et le cytoplasme de la cellule vers la périphérie, devenant une couche fine. Ainsi au microscope, cette cellule peut ressembler à une bague. L'adipocyte ne peut pas se dupliquer, il dérive d'une cellule pré-adipocytaire. Lorsque l'adipocyte est saturé en triglycéride et arrive à sa taille critique, les cellules précurseur d'adipocytes (les pré-adipocytes) sont stimulées, entraînant leurs divisions puis leurs différentiations en adipocytes. Ainsi le nombre d'adipocytes du corps augmente. Cette transformation est favorisée par la suralimentation sur une longue période de temps et est ralentie par l'activité physique. Une fois formé, l'adipocyte reste à sa place de façon permanente. Seule une réduction de la taille de la cellule est possible (Albright *et* Stern, 1998) notion essentielle dans la compréhension des rechutes après perte de poids chez les obèses.

La prise alimentaire, la lipogénèse et la lipolyse sont sous l'influence de nombreux facteurs notament l'insuline, la leptine et la ghréline. Les facteurs lipolytiques les plus importants sont thyréostimuline (THS), l'adrénaline, le glucagon, la somatotrophine, l'hormone adrénocorticotropique (ACTH), et les hormones thyroïdiennes. Les facteurs lipogéniques sont essentiellement l'insuline et les estrogènes (Bacci et Leibaschoff, 2006).

PARTIE 3 : LES STAREGIES DE PERTE DE POIDS DISPONIBLES AU GRAND PUBLIC SANS ORDONNANCE MEDICALE

Il existe de nombreuses façons de mincir. Cette thèse explore uniquement les stratégies de perte de poids disponibles sans ordonnance médicale. La chirurgie et les médicaments ne seront pas abordés ; les crèmes topiques non plus. En revanche, dans cette partie de thèse, nous aborderons le marketing autour de l'industrie de la minceur ainsi que l'activité physique et deux méthodes de régime parmi les plus répandues sur le marché pour lesquelles nous détaillerons les risques associés.

L'activité physique

L'activité physique et le métabolisme basal (l'énergie consommée par le corps lorsqu'on est au repos) constituent les deux sources de dépenses énergétiques. Plus on fait de l'exercice, plus on acquiert de la masse musculaire et plus le métabolisme basal est augmenté car le muscle consomme plus d'énergie que la graisse au repos (Xiao *et* Yang, 2012).

Le souci de nombreux régimes est qu'ils entrainent une perte de poids constituée en grande partie de cette masse musculaire, ce qui diminue donc le métabolisme basal et perturbe la balance énergétique. Une fois la masse musculaire et le métabolisme basal réduits, la seule façon de les augmenter à nouveau est de reconstituer sa masse musculaire en faisant de l'exercice régulier tel que le vélo, la marche rapide, et le jogging (Binnert *et* Tappy, 2001).

Les régimes

Les études montrent qu'une personne sur trois a suivi un régime en 2010 en France (Pichon, 2012). L'obésité et le surpoids étant essentiellement le résultat d'un déséquilibre entre l'énergie apportée par l'alimentation et l'énergie consommée par le corps, une réduction des apports caloriques est généralement nécessaire pour réduire son poids corporel. Dans cette thèse, il a été choisi d'étudier le régime Dukan pour sa forte popularité en France ainsi que le régime Weight Watchers qui bénéficie de preuves scientifiques concernant son efficacité.

Le régime Dukan

Le régime Dukan a été créé par le nutritionniste français Docteur Pierre Dukan. Il serait suivi par environ 25 millions d'adeptes dans le monde (Pichon, 2012). C'est un régime hyper protéiné, cétogène, pauvre en lipides (dont la proportion est légèrement inferieure aux apports nutritionnels conseillés), pauvres en glucides (11 à 19% des apports nutritionnels conseillés) et non hypocalorique (1800 Kcal/jour en moyenne) (Houille Lepigeon, 2011). Ce régime reproduit les caractéristiques d'un jeûne en forçant le corps à brûler les réserves lipidiques plutôt que les glucides alimentaires. Le manque de glucides alimentaires conduit à la production de cétones par le foie. Ces cétones peuvent être utilisées comme substrats énergétiques par le cerveau en période de jeûne ou de famine.

C'est un régime basé sur 4 phases. La première est la plus stricte et la plus hypocalorique (apportant uniquement 50% des apports nutritionnels recommandés). Pour cela, seules des protéines maigres peuvent être consommées pendant les 5 premiers jours. Le moindre écart peut être avoir un effet negatif pour le régime car il faut quelques jours pour que le corps mette en place la synthèse des cétones. Cette production de cétones est due au manque de glucides, qui est l'aliment du cerveau. Certains effets secondaires sont associés à cette phase

(ex : mauvaise haleine, fatigue, maux de tête, étourdissements, nausées, insomnies, difficultés pour se concentrer, reprise de poids lors de la consommation de glucides, etc…). La seconde phase autorise la réintroduction d'une liste restrictive de légumes. Celle –ci peut durer plusieurs semaines (1 semaine par kilogramme) voire des mois en fonction du poids que la personne cherche à perdre. La troisième phase est la phase de consolidation qui dure 10 jours par kilogramme perdu, elle vise à réintroduire progressivement des aliments contenant des glucides et des lipides. Mais encore une fois la liste des aliments autorisés est stricte et restrictive. La dernière phase est la phase de stabilisation qui est **à vie**. Dans cette phase, il faut s'alimenter une journée par semaine de protéines pures, comme au cours de la phase 1. Il faut également consommer une cuillère à café de son d'avoine tous les jours pour apporter des fibres solubles, à même de moduler l'absorption des sucres et des graisses. (Dukan Diet Official Site, 2013; Houille Lepigeon, 2011 ; Pichon, 2012).

Ce type de régime devrait être réservé aux personnes dont l'obésité menace leur santé et dont le poids à perdre est très important, et ce en dernier recours après un échec de perte ou de stabilisation de poids suite à la mise en place de mesures hygiéno-diététiques saines et équilibrées au préalable. C'est un régime facile à comprendre, sans limite dans la quantité des aliments consommés, conduisant à la perte rapide de masse graisseuse. Cependant, ce régime est extrêmement strict et il conduit fréquemment à des abandons dus à la monotonie de l'alimentation restreinte en terme de choix et aux effets secondaires pouvant être très importants. Les effets secondaires peuvent être ceux cités dans l'explication de la phase 1, mais également la constipation, les maux de ventres, des hémorroïdes (liés au manque de fibres alimentaires), une cholélithiase, des crises de goutte, de l'hypotension orthostatique, une perte de cheveux et une sécheresse cutanée (dues à un manque d'acides gras essentiels), une sensation de froid, des crampes musculaires, etc… (Houille Lepigeon, 2011 ; Pichon, 2012). De plus, ce régime nécessite une consommation importante d'eau afin de limiter les dommages que l'élimination de l'excès de protéines pourrait avoir sur les reins. Deux autres effets secondaires peuvent être révélés après le commencement de cette méthode : la dépendance à vie envers ce régime et le risque important de reprise de poids suite à la consommation de féculents.

Il faut savoir que 95% des personnes qui suivent un régime (et en particulier ce régime Dukan) reprennent par la suite le poids qu'elles ont perdu voire même davantage dans les deux ans en moyenne. Il est donc intéressant d'éviter de changer ses habitudes alimentaires de plus de 20%, ce qui permet d'encourager la perte ou la stabilisation de poids de façon lente et durable, boostée par de l'activité physique régulière.

Le régime Weight Watchers

Ce régime a été crée il y a 50 ans. Chaque semaine en France, il y a 1200 réunions Weight Watchers et 120 000 adhérents à la méthode. C'est un régime très équilibré, hypocalorique

(1200 à 1500 Kcal/jour), hypolipidique (25% des apports énergétiques totaux), légèrement hyperprotéique (20% des apports énergétiques totaux) et normoglucidique (55% des apports énergétiques totaux).

La méthode est basée sur l'éducation alimentaire et le renforcement de la motivation. Pour cela, la méthode comprend des réunions hebdomadaires qui ont pour but de soutenir, motiver et enseigner aux clients la méthode et un système de comptage de calories sous forme de points avec un quota de points maximums par jour et par semaine. Chaque aliment vaut un certain nombre de points et le quota journalier et hebdomadaire est proposé en fonction de chaque individu selon sa taille, son poids, son âge et son sexe (Collectif, 1999; Collectif, 2004; Houille Lepigeon, 2011; Pichon, 2012).

Des menus et des recettes sont proposés pour faciliter le suivi de la méthode. De plus, un programme d'exercices physiques personnalisés est proposé en fonction des aptitudes de chacun. Un des avantages de cette méthode est l'accompagnement personnalisé et l'éducation nutritionnelle qui permettent une meilleure adhésion à la méthode. De plus, aucun aliment n'est banni donc chacun peut manger et boire ce qu'il veut à condition de respecter son quota de points. Cette méthode apprend à acheter, à cuisiner et à manger des repas équilibrés et sains. Elle donne de bonnes habitudes pour la période de perte de poids mais également pour la suite, évitant une reprise de poids (Collectif, 1999; Collectif, 2004; Houille Lepigeon, 2011; NHS choices, 2011; Pichon, 2012). Les quelques inconvénients de cette méthode sont les suivants : il n'y a pas de suivi médical des clients, elle peut paraître coûteuse pour certains et elle suppose une certaine disponibilité pour assister aux réunions et comprendre le système de points. Ceci-dit, cette méthode permet d'acquérir de bonnes fondations pour transformer ses habitudes alimentaires de façon durable et saine.

Risques de la perte de poids

L'ANSES (L'Agence National pour la SEcurité Sanitaire) a écrit un rapport concernant les risques des différentes méthodes de perte de poids. Les résultats montrent que tous les régimes peuvent avoir des effets secondaires néfastes et sont souvent inefficaces. Le simple fait de perdre massivement du poids peut avoir des conséquences pour la santé. Les principaux risques incluent :

- La perte de masse musculaire
- La perte de densité osseuse
- Un risque pour le foie et les reins
- Des risques au niveau psychologique et comportemental.

En effet, les régimes peuvent conduire à une perte de confiance en soi, en particulier si la personne n'arrive pas à mincir ou à stabiliser son poids. Dans 80% des cas, les personnes

reprennent une partie du poids dans l'année suivant leur régime. Presque tous reprennent la totalité du poids perdu dans les 5 années qui suivent.

Le fait de faire continuellement des régimes sans surveillance médicale peut mener à d'importantes complications sur le long terme. Celles-ci peuvent se traduire par une inflammation hépatique, l'accroissement des polluants organiques libérés par le corps (pouvant avoir des conséquences endocrines, métaboliques, reproductives et sur le système immunitaire) et peuvent conduire ainsi à l'accroissement pondéral et à des problèmes de santé, et dans des rares cas à une mort soudaine (Pichon, 2012).

L'OMS propose quelques conseils pour avoir un mode de vie sain : manger quotidiennement de nombreux fruits et légumes, réduire la consommation de gras, sucre et sel, faire de l'exercice physique régulièrement et calculer son IMC pour surveiller son poids.

Pour conclure, tout régime avec une perte de poids importante devrait être individualisé, suivi par un professionnel de santé, accompagné de mesures diététiques équilibrées et comportant un programme d'activités physiques adaptés.

PARTIE 4 : LES PRINCIPES ACTIFS DES COMPLEMENTS ALIMENTAIRES MINCEURS.

Dans notre société actuelle, le culte de la minceur explique que les stratégies de perte de poids et de régimes alimentaires sont si prédominantes. Cette quête du corps parfait oblige les professionnels de santé à faire face aux nouvelles pratiques telles que la consommation de compléments alimentaires pour tenter de perdre du poids. Les compléments alimentaires sont définis comme étant « des denrées alimentaires dont le but est de compléter le régime alimentaire normal et qui constituent une source concentrée de nutriments ou d'autres substances ayant un effet nutritionnel ou physiologique seuls ou combinés, commercialisés sous forme de doses, à savoir les formes de présentation telles que les gélules, les pastilles, les comprimés, les pilules et autres formes similaires, ainsi que les sachets de poudre, les ampoules de liquide, les flacons munis d'un compte-gouttes et les autres formes analogues de préparations liquides ou en poudre destinées à être prises en unités mesurées de faible quantité » (décret n°2006-352, 2006).

Les compléments alimentaires minceur sont très répandus mondialement, particulièrement en France. Ils peuvent être trouvés en pharmacie, en parapharmacie, en boutiques diététiques, dans les grandes et moyennes surfaces ainsi que sur internet. Ces produits promettent par exemple d'affiner la silhouette, d'obtenir un ventre plat, d'éliminer la cellulite, de perdre du poids, etc... Sont-ils tous efficaces ? Comment choisir celui qui est le plus adapté à sa recherche ? Quels sont les contre-indications et les effets secondaires de chacun ? Pour répondre à ces questions, le pharmacien a un rôle important à jouer pour conseiller et protéger ses patients.

Si l'on fait abstraction des substituts de repas hypocaloriques et des diètes semi-protéinés non traitées ici, les ingrédients que contiennent les compléments alimentaires minceurs entrent généralement dans l'une des catégories suivantes : les « capteurs de graisses » tels que le chitosan, les actifs « anti-sucre» tels que le chrome, les « drainants et détoxifiants » tels que l'orthosiphon, les « agents thermogènes » tels que le thé vert, la caféine, le maté et le guarana ainsi que les actifs renfermant des fibres solubles parfois nommées « satiétants » tels que le glucomannane.

Dans cette thèse, un exemple de chaque classe est illustré sous forme de tableau récapitulatif comprenant pour chaque ingrédient actif :

- Les principaux composants responsables de l'activité
- Les sources de celui-ci
- Le mécanisme d'action supposé
- Les effets secondaires possibles
- La toxicité
- Les contre-indications et possibles interactions
- Des exemples de produits finis

Une attention plus particulière a été portée à l'étude du thé vert et du glucomannane du fait des preuves scientifiques concernant leur efficacité dans la perte de poids.

Le thé vert

Le thé vert provient des jeunes feuilles desséchées du théier (*Camellia sinensis*, Theaceae). Cet extrait est un thermogénique, ce qui signifie qu'il augmente la production de chaleur par le corps, augmentant ainsi la béta-oxydation des acides gras du tissu adipeux. Les ingrédients thermogéniques augmentent alors le métabolisme basal du corps, favorisant une balance énergétique négative et donc la perte de poids (Bertrand, 2011; Grove *et* Lambert, 2010 ; Hursul *et al.,* 2009).

Chimiquement, cette plante sèche est caractérisée par la présence d'une grande quantité de composés polyphénoliques antioxydants : les flavonoïdes aussi connus sous le nom de flavan-3-ol ou catéchines. La catéchine la plus pharmacologiquement active et le plus représentée dans la plante est l'EGCG (Epigallocatéchine gallate). Le thé vert contient également de la caféine, thermogénique, et de la théophylline, diurétique, (Bertrand, 2011; Grove *et* Lambert, 2010). Une tasse de thé vert contient en moyenne 50 mg de caféine et 80 à 100 mg de polyphénols.

Dans les pays occidentaux, la consommation de thé vert s'est largement développée durant la dernière décennie, notamment grâce aux nombreuses propriétés qui lui sont attribuées,

en particulier concernant la perte de poids. Les résultats des études cliniques au sujet des compléments alimentaires contenant un extrait de thé vert montrent souvent des pertes de poids significatives. Par ailleurs, les doses de polyphénols contenus dans les extraits ne doivent pas être excessives de manière à réduire le risque potentiel d'hépato-toxicité. Il est également recommandé de limiter sa consommation de thé vert ou d'en consommer de façon très modérée pour les patients prenant des anticoagulants, des antidépresseurs, des antipsychotiques, de la phenytoine, ou des fluoroquinolones, de même que pour les sujets végétariens, les femmes enceintes, ou les personnes sous chimiothérapie. La recherche soutient globalement l'hypothèse que le thé vert pourrait avoir un effet bénéfique sur la perte et la stabilisation du poids. Cependant, cet effet dépendrait grandement du dosage en EGCG et en caféine, des habitudes du sujet (consommation régulière de caféine ou non) voire même de son origine ethnique (Caucasien vs. Asiatique).

Le glucomannane

La réduction de l'apport alimentaire est l'une des méthodes les plus efficaces pour perdre du poids. Les compléments alimentaires réduisant la sensation de faim en accroissant la sensation de satiété peuvent être très bénéfiques lors de régimes hypocaloriques. Les satiétants sont généralement des substances riches en fibres, hydrophiles pouvant absorber de grandes quantités d'eau, et provenant de plantes, algues, ou écorces de fruits.

Le glucomannane fait justement partie de la famille des satiétants aussi appelés réducteurs d'appétit. C'est une fibre soluble, extraite d'une plante de la famille des Aracées, l'Amophorphallus konjac, cultivée dans l'Est de l'Asie. Le tubercule (racine) de cette plante est séché et broyé, se transformant en une farine composée principalement de mucilage neutre tel que le glucomannane. Le glucomannane est consommé en Asie depuis plus de 1000 ans (Walsh et al., 1984).

Le glucomannane, polysaccharide et fibre alimentaire de haut poids moléculaire (200-2000 kDA) n'est pas dégradé par les enzymes digestives de l'estomac et de l'intestin grêle de l'Homme (AFSSA, 2002; EFSA Journal, 2010).

Il a été montré que l'obésité est moins prévalente dans les populations consommant de grandes quantités de fibres alimentaires (Newby *et al.,* 2005). Le glucomannane peut être une aide intéressante à la perte de poids pour les personnes en surpoids, obèses, ou ayant un appétit excessif. Il gonfle dans l'estomac en absorbant l'eau du bol alimentaire, formant une masse gélatineuse avec une très haute viscosité provoquant une distension de l'estomac favorisant ainsi l'apparition de la sensation de satiété. Cette masse visqueuse va ralentir la progression du bol alimentaire dans le tractus digestif ralentissant alors la vidange gastrique. La quantité de calories absorbée est également réduite du fait de l'emprisonnement des lipides et des glucides dans la masse visqueuse.

Grâce à ses propriétés mécaniques et à sa capacité à provoquer la satiété après ingestion, la prise de glucomannane est une façon intéressante de soutenir un régime hypocalorique. Ainsi, l'EFSA (Europeen Food and Safety Authority) reconnaît que le glucomannane contribue à la réduction du poids corporel, à la condition qu'au moins 3 grammes soient consommés par jour (en trois fois) avec un grand verre d'eau avant chaque repas dans le contexte d'un régime hypocalorique. Pour arriver à cette conclusion, le panel EFSA a étudié plus de 45 études cliniques et références scientifiques.

Avant de proposer un complément alimentaire à base de glucomannane, le pharmacien doit s'assurer que le patient ne présente pas de douleurs abdominales, et n'a jamais eu d'occlusions intestinales dans le passé. De plus, il doit toujours le proposer en parallèle d'un régime hypocalorique et en association avec de l'exercice physique régulier ainsi qu'une bonne hydratation.

CONCLUSION

Cette thèse explore un vaste éventail d'options sans prescription médicale et disponible aux patients en surpoids ou obèses pour perdre du poids. De nombreuses conclusions peuvent être émises :

Tout d'abord, nous vivons dans une société dictée par l'image de soi, par le fait d'être mince d'avoir un corps parfait. Malheureusement, les images publicitaires qui nous entourent ne reflètent pas la réalité. En effet dans celles-ci plus de 95% des femmes ont une corpulence normale ou maigre contrastant avec la « vraie vie » où 55% des adultes européens en sont en surpoids ou obèses. La contradiction entre la réalité et l'image idéale des hommes et des femmes est très marquée et elle nourrit l'industrie de la minceur.

Les différents éléments étudiés lors de cette thèse, laissent penser que très souvent, il est plus bénéfique pour un patient en léger surpoids de stabiliser son poids plutôt que de chercher à perdre du poids à tout prix. Insistons bien que cet adipocyte une fois installé dans le tissus adipeux, le restera à vie. Sa taille pourra varier mais il ne disparaîtra pas. De plus, si le corps subit une période de privation, il peut engendrer une réduction du métabolisme basale (par perte de masse musculaire par exemple), déséquilibrant la balance énergétique et donc favorisant par la suite un accroissement de stockage de graisse lors de la reprise d'apports énergétiques normaux.

Un régime devrait toujours être individualisé et adapté au style de vie, à l'historique de la personne, à sa culture, ainsi qu'à son contexte psychologique et comportemental. Il est recommandé qu'un régime soit suivi par un professionnel de santé compétent. Il est également essentiel d'éviter les changements drastiques d'habitudes alimentaires et d'éviter l'exclusion complète d'une catégorie d'aliments. De nombreuses méthodes pour maigrir

existent mais elles ne sont pas toutes saines, efficaces et sûres à long terme. Parmi ces méthodes, le régime Dukan, du fait de la carence en glucides, peut induire une perte de poids rapide mais aussi reprise de poids suite au retour à une alimentation normale. L'excès de protéines qu'il recommande peut être néfaste pour les reins à long terme. Le régime Weight Watchers, au contraire, enseigne des habitudes alimentaires saines et motive les participants avec cependant certains inconvénients, tels que le prix ou l'absence de suivi médical. De manière à «booster» une réduction ou une stabilisation d'IMC, certaines aides existent. Cette thèse insiste en particulier sur les compléments alimentaires minceurs tels que le thé vert et le glucomannane qui sont deux ingrédients actifs souvent retrouvés dans ces produits. Leur efficacité dans l'accompagnement de la perte de poids a été scientifiquement démontrée à condition cependant de respecter certaines précautions d'emploi, et notamment être vigilant concernant les risques potentiels de toxicité ou d'effets secondaires et d'employer des doses suffisantes pour obtenir des effets significatifs. Pour autant, ils ne doivent pas être considérés comme miraculeux et n'entrainent que des pertes de poids relativement faibles. Les compléments alimentaires minceur sont donc plutôt destinés aux personnes en léger surpoids et doivent être pris en parallèle de mesures alimentaires saines et hypocaloriques ainsi que de l'exercice physique.

ABREVIATIONS

ACTH: Adrenocorticotropic hormone

AFSSA: Agence Française de Sécurité Sanitaire des Aliments (French agency for food health and safety).

ANSES: Agence Nationale de Sécurité Sanitaire de l'Alimentation, de l'Environnement et du Travail (French Agency for Food Environmental and Occupational Health & Safety).

AT: adipose tissue

ATP: Adenosine Triphosphate

BP = Blood pressure

BMI : body mass index

cAMP: cyclic Adenosine Monophosphate

CETP : Cholesteryl ester transfer protein

CoA: Coenzyme A

COMT: Cathecol-O-Methyl-Transferase

CRP: C-Reactive Protein

DGCCRF : Direction Générale de la Concurrence, de la Consommation et de la Répression des Fraudes (The french General Directorate for Fair Trading, Consumer Affairs and Fraud Control)

EC : epigallocatechin

ECG: epicatechin gallate

EFSA: European Food Safety Authority

EGCG : epigallocatechin gallate

FFAs: free fatty acids

FPG = Fasting plasma glucose

HAS: Haut Autorité de Santé

HDL = High density lipoprotein

HSL: Hormone Sensitive Lipase

IL-6: Interleukin-6

IMC : Incide de masse corporelle

INSEE : France's National Institute of Statistics and Economic Studies (Institut National de la Statistique et des Études Économiques)

LPL: Lipoproteine Lipase

MAO: Monoamine Oxidase

NA: Noradrenalin

PAL-1: Plasminogen Activator Inhibitor-1

PKA: Proteine Kinase A

RDA: Recommended Daily Allowance

TG: Triglycerides

TNF- α: Tumor Necrosis Factor-α

TSH: Thyroid-Stimulating Hormone

UCP1: Uncoupling Protein 1

VLDL: Very Low Density Lipoproteins

VLDL-c: Very Low Density Lipoprotein-Cholesterol

WHO: World Health Organization

INTRODUCTION

The number of people around the world whose body weight is greater than their ideal is increasing. The thin perfect body that media has been developing for the past 40 years is in contradiction with the epidemic of overweight and obesity globally. The WHO (World Health Organization) describes obesity as being one of the most blatantly visible, yet most neglected, public-health problems that threatens to overwhelm both more and less developed countries (WHO, 2000). Indeed, obesity is now recognized as a chronic disease and the second leading cause of preventable death, exceeded only by cigarette smoking (Das, 2010).

The presence of an imbalanced diet and a sedentary life style increase energy intake and decrease energy expenditure which promotes overweight alongside with numerous other factors. This thesis explores overweight, the adipocyte as well as a broad spectrum of non-prescription weight loss strategies available to consumers. In particular the Weight Watchers and Dukan diet will be explored as well as the active ingredients commonly found in dietary supplements, notably green tea and glucomannan.

It is important that the pharmacist clearly understands the problematics linked to overweight and obesity as well as the needs and desires of overweight and obese patients in order to orient them and advise them more efficiently.

PART 1: OVERWEIGHT AND OBESITY

1. Definition and prevalence

1.1 Definition

Overweight and obesity are defined by the WHO as **abnormal or excessive fat accumulation that may impair health**. A measurement called the body mass index (BMI) is commonly used to determine if someone is overweight or obese. It is calculated as patient's weight measured in kilograms (kg) divided by the square of the patient's height measured in meters (m), expressed as kg/m² (Ciangura *et al.*, 2010).

$$\text{BMI} = \frac{\text{Weight Kg}}{\text{Height}^2\ \text{m}^2}$$

The world health organization (WHO) also defines overweight in adults (aged at least 19 years old) as having a BMI of 25-30 kg/m² and obesity as having a BMI equal to or greater than 30.0 kg/m² (WHO, 2012 a). A person with a BMI above 40 is characterized by the term morbid obesity (Chevallier, 2011; WHO, 2012 a; WHO, 2013).

Classification	BMI (kg/m^2) cut-off points
Underweight	<18.50
Normal range	18.50 - 24.99
Overweight	25 – 29.99
Obese	≥30.00

Figure 1: The international classification of adult underweight, overweight and obesity according to BMI (WHO, 2013)

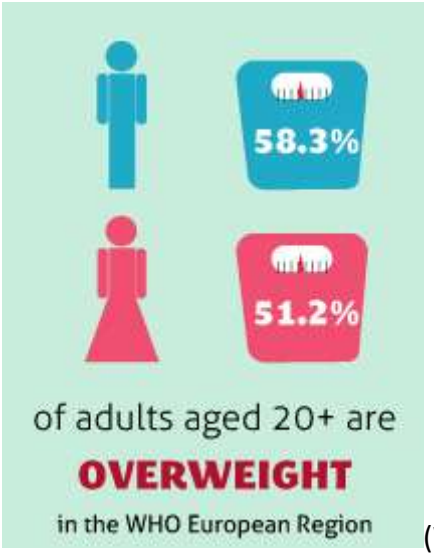
BMI values are age-independent and the same for both sexes. However, BMI may not correspond to the same degree of fatness in different populations notably due to different body proportions. The health risks associated with an increasing BMI are considered as continuous. In addition, the interpretation of BMI gradings in relation to risk may differ for different populations (WHO, 2013).

The WHO, taking into account the worldwide epidemic development of obesity and its adverse consequences, decided to define obesity as a disease in 1997 (WHO, 1997).

1.2 Prevalence

Obesity can be considered as a worldwide epidemic. It has more than doubled since 1980 (WHO, 2012 b). The obesity epidemic has grown universally in countries both rich and poor, and among all segments of society. Worldwide, more than 1.4 billion adults aged 20 and older were overweight in 2008. Of these, over 500 million were obese.

In the WHO European Region, the age-standardized prevalence of overweight was 58.3% among adult males and 51.2% among adult females (WHO, 2012 a).



(WHO, 2012 a)

In the United States more than half of the adult population was classified as overweight or obese in 2000. On the basis of a normal BMI ranging from 18.5 to 24.9, 31% of the US adult population was obese, and an additional 34% was overweight (Pittler *et* Ernst, 2004).

Future obesity for adults in the United States is projected on the basis of National Health and Nutrition Examination Study. By 2030, 86.3% American adults are expected to be overweight or obese; of which 51.1% obese. Total health-care costs attributable to obesity/overweight are planned to double every decade up until 2030, accounting for 16–18% of total US health-care costs (Wang *et al.*, 2008).

The rising overweight and obesity epidemic reflects the profound changes in society and in the behavioral patterns of communities although some individuals may become obese, partly because they have a genetic or other biological predisposition to gain weight more readily when they are exposed to an unfavorable environment. The widespread decline in physical activity in most societies, combined with rising fat intake, are notably associated with rapidly rising rates of obesity (WHO, 2000).

2. Causes

The fundamental causes of the obesity epidemic are **high-fat, energy-dense diets and sedentary lifestyles.** These two principal factors tend to overwhelm an individual's normal subconscious adjustments to food intake and his or her metabolism. These factors have an influence on the biological capacity to maintain an energy balance. Indeed the fall in spontaneous and work-related physical activity, and the tendency to over consume high-fat, energy-dense foods can lead to weight gain (WHO, 2000).

As seen above, obesity is defined medically as an increase in adipose tissue or body fat, deleterious to health. This excess of fatty tissue attests to the incapacity of the body's energy regulatory systems to deal with the environmental factors, eating behavior patterns, and various psychological, biological, genetic and neuro-hormonal dysfunctions. At one end of the spectrum, there are forms of obesity that are purely biological or genetic while at the other, there is purely behavior-related obesity (Ciangura *et al.*, 2010). In sum, body weight is ultimately determined by a multitude of factors notably by the interaction of genetic, environmental, physiological and psychosocial factors (Marti *et al.*, 2004).

2.1 Evolution of dietary habits

Dietary habits in populations from industrialized countries have been considerably altered during the second half of the 20th century. The daily caloric portion has considerably increased, while at the same time the energy expenditure has decreased (as will be explained in chapter 2.3 "Decrease in energy expenditure.")

A change in eating patterns has also been observed: skipping meals, snacking, increase in the consumption at fast food restaurants, etc. These dietary modifications are also qualitative: excessive consumption of foods rich in fats (cheese, fatty meats, sauces, readymade dishes also known as convenience food, etc.) sugars and fast-release carbohydrate while decreasing the consumption of dietary fiber and slow release carbohydrates (Invs, 2005). As an example, one gram of lipids contains more than the double of calories than a gram of proteins or glucids (Bertrand, 2011), which implies that the change in dietary habits can have important impacts on body weight. In certain cultures alcohol consumption is relatively high and can also contribute to the increase in energy intake (Invs, 2005). All these elements contribute to the expansion of obesity in all age groups.

2.2 Excess energy intake

Overeating plays a major role in obesity, but not all foods eaten in excessive amounts lead to metabolic consequences.

Despite substantial fluctuations in daily food intake, healthy humans maintain a remarkably stable adiposity and body weight. Indeed the overall caloric ingestion and expenditure are matched over long periods of time, through the process of energy homeostasis. This process stabilizes the amount of body energy stored as fat. Although the body has an efficient system to regulate body weight according to food intake, an excess of energy intake by less than 1%, compared to the daily energy expenditure, can lead to a detrimental increase of body weight and metabolic complications in the long term (several years). Consequently, all the mechanisms influencing calorie ingestion and subsequent harvesting should contribute to the balance of the body weight (Cani *et* Delzenne, 2009). **Excess food intake compared to the body's needs is one of the most determinant factors in the development of obesity regardless of genetic predisposition or other factors.**

Three studies including over 120 000 individuals were combined to determine the causes of weight gain in time. The three studies were: Nurses' Health Study (NHS), followed for 20 years (1986 to 2006); Nurses' Health Study II (NHS II), followed for 12 years (1991 to 2003); and Health Professionals Follow-up Study (HPFS), followed for 20 years (1986 to 2006).
These studies put forward the impact of dietary habits and way of life on weight gain though out the years. The possible associations were evaluated every four years during 12 to 20 years, according to the study. Weight gain was of 1.5 kg every four years (representing an increase of 2.4 percent of total weight) with extremes of -1.8 to +5.6, which represents a weight gain of 7.6 kg in 20 years. The influence of dietary factors on weight gain is illustrated below (Mozaffarian *et al.*, 2011).

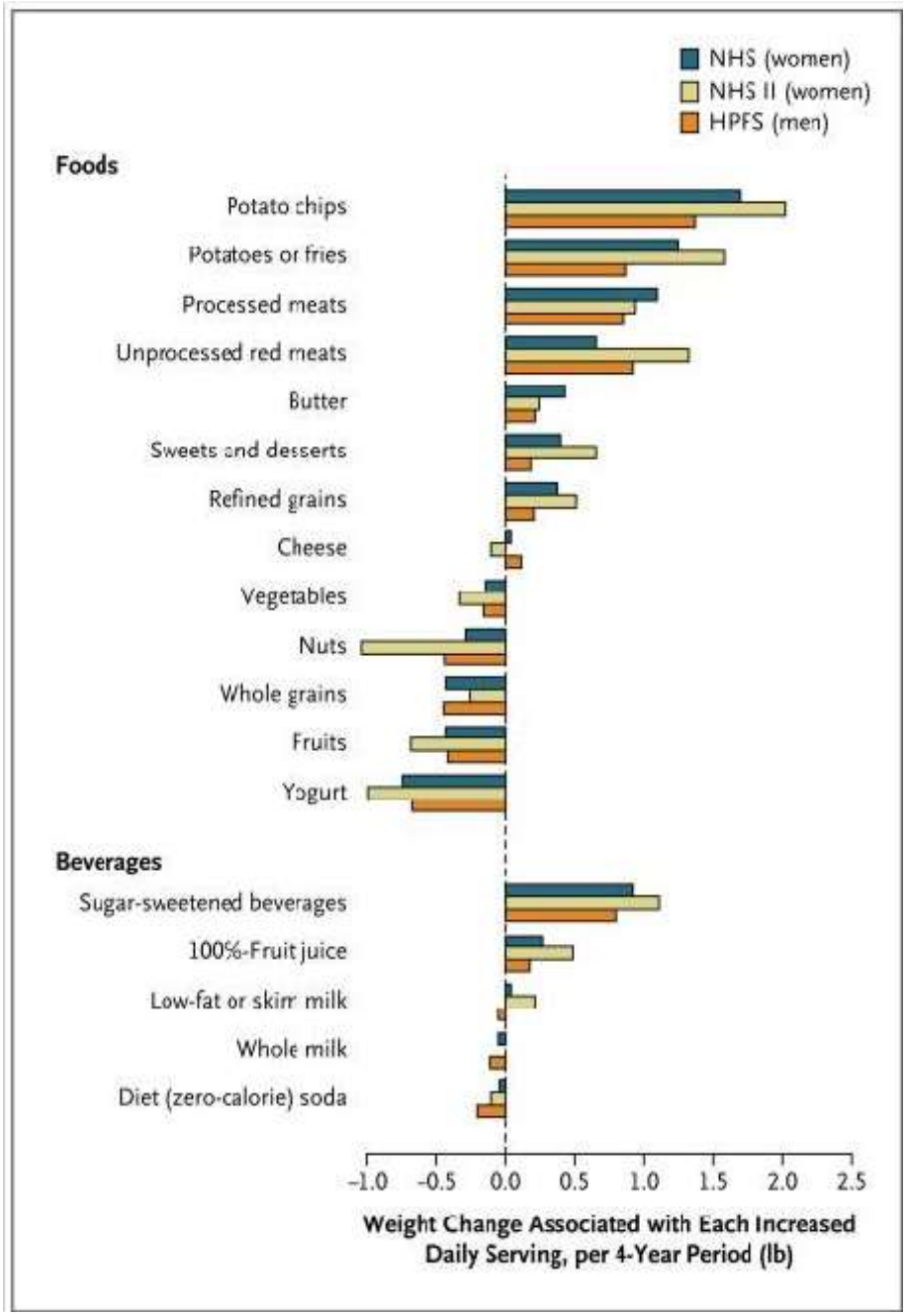


Figure 2: Relationships between changes in food and beverage consumption and weight changes every 4 years, according to study cohort (Mozaffarian et al., 2011).

The subjects who did the most physical activity gained about 800 grams less every four years. The factors that increase weight gain in time were alcohol consumption (+185g in four years for at least one glass per day), quitting smoking (+ 2,3kg), less than six or more than eight hours of sleep per night, and the time spent in front of the television (+150g in four years for at least one hour per day)(Mozaffarian *et al.*, 2011).

All these individual factors can add up and contribute to weight gain in time (Mozaffarian *et al.*, 2011).

2.3 Decrease in energy expenditure and physical activity

The energy balance is the ratio of energy intake on energy expenditure. The energy expenditure is composed of the resting metabolic rate, thermogenesis and physical activity.

2.3.1. Resting metabolism rate

Energy homeostasis is ensured by regulatory mechanisms that tend to vary according to food intake and energy expenditure in order to compensate positive or negative deviations in the energy balance (Binnert *et* Tappy, 2001).

Even when we are resting we burn calories in order to sustain basic body functions such as respiration and digestion. The resting metabolic rate or basal metabolism determines how much energy we use when staying still. The basal metabolism represents 60 to 75% of our total energy consumption and physical activity represents about 15 to 30 % of the total consumption. The rest of the energy, about 10 percent is used for thermogenesis (increase of the body temperature after food intake). In order to keep a stable body weight during a long period of time it is crucial to maintain a neutral energy balance (Binnert *et* Tappy, 2001). The resting metabolic rate slows when aging or when losing weight quickly. Typically, athletes or people with more muscle and less fat have higher metabolic rates than those with less muscle and more fat, because muscle has higher energy requirements than fat tissue. Indeed, adipose tissue composes approximately 20% of body weight but its rate of oxygen utilizing in the basal state is less than 2% of whole body rate of oxygen consumption (Frayn et al., 1995). The more muscle mass a person builds through exercise, the more calories his or her resting metabolism requires (Binnert *et* Tappy, 2001). Thermogenesis is a mechanism that produces body heat and thermoregulation. The heat is generated by the beta-oxidation of fatty acids from the adipose tissue (Cottin, 2011).

If energy intake is superior to energy expenditure, the balance is considered as positive, which long term can cause weight gain. An excess in energy intake can also be due to someone who eats more than necessary, doesn't exercise enough, or more rarely can be liked to a metabolic disorder (Binnert *et* Tappy, 2001).

2.3.2 Decrease in physical activity

The decrease in energy expenditure can be explained by our modern day sedentary lifestyle and work habits. The sedentary patterns are facilitated by motorized transportation, better heating in residential areas and offices, decrease in physical activities and other common physically inactive pursuits (TV viewing, computer work, etc) and have markedly risen in the last decades (Marti *et al.*, 2004).

(WHO, 2012 a)

Weight gain can become a viscous circle since weight gain makes exercise more complicated and thus can discourage doing physical activity which in turn promotes weight gain, etc.

Although physical activity is not the major component of the total energy expenditure, it is the factor that is easiest to modulate. The more we exercise the more calories we burn each day (Heymsfield *et al*., 2011). Exercise has best results in weight loss when coupled with healthier eating habits.

2.4 Genetic predisposition

Body weight stability and the associated regulatory processes are dependent of nutrient intake, but are also influenced by genetic-dependent metabolic and neuro-endocrine mechanisms (Marti *et al.*, 2004). The genetic influence of the differences in energetic metabolism, from an energy intake or expenditure point of view, in different subjects, is not well-known today (Sherwood, 2006).

Cases of obesity caused by a single gene mutation, for example, the mutation of the gene coding for the leptin receptor, are very rare and can be counted on the fingers of one hand (Sherwood, 2006).

The commonly observed coexistence of several obese members within a family can suggest the involvement of genetic factors in obesity. Moreover, twin and adoption studies have shown the influence of genetics in obesity. To illustrate further, the discovery of populations such as Pima Indians with shared alterations in basal metabolism rates or in fat oxidation after food intake feeds the hypothesis of the influence of genetics in obesity as well as the fact that genetic factors could modulate the effects of physical activity and diet on weight and body composition. However, this information is not sufficient to completely prove the genetic origin of obesity, since families share other factors implied in obesity such as lifestyle, dietary habits and environment (Marti, 2004).

The possible mechanisms through which the genetic susceptibility could act include reduced rates of basal metabolism and macronutrients oxidation, alterations of adipogenesis and quantitative and qualitative deviations of food intake. Also, other factors could be specifically involved in the genetic processes affecting the energy balance equation such as the hormonal profile, energy exercise efficiency and thermogenesis (Marti *et al.*, 2004).
Certain publications go as far as saying that the rapid increase in obesity incidence over recent years suggests that environmental and lifestyle influences, as well as other physiopathological or genetic determinants, are independently affecting the energy balance equation adjustment. Thus, they estimate that 40–70% of the variation in BMI is heritable, while they believe cultural and societal factors may explain at least 30% of the variation (Marti *et al.*, 2004).

2.5 Gut microbiota

The gut microbiota is inherited from our mothers, mainly at birth. Its composition influences nutrient absorption after food intake. It has been show that the gut microbiota of obese and lean individuals is different.

Nearly 10 years ago, a group of American researchers discovered that gut microbiota composition is involved in the regulation of energy homeostasis (Hooper *et al.,* 2002). Later, the impact of obesity on gut microbiota composition was published in 2006 by Gordon's group. They demonstrated that the presence of a larger proportion the bacteria phylum Firmicutes and relatively fewer Bacteroidetes in obese individuals' microbiota when compared with lean subjects (Ley *et al.*, 2006). In addition, in preclinical studies researchers showed that the intestinal flora plays a key role in weight loss by demonstrating that energy harvesting from food was influenced by the microbiota (Ley *et al.*, 2005).

Several studies have proposed that modulation of gut microbiota could regulate fat storage and body weight.

In preclinical experiments, Backhed *et al.* found that the mice raised in the absence of microorganisms (germ free) had about 40% less total body fat than those with a normal gut microbiota, even though they later ate 30% less of the same chow diet than did the germ free control mice. To get more insight to these findings, the authors performed a key experiment: they transferred a normal gut microbiota to the gut of germ-free mice, and found that it induced a 60% increase in body fat content and insulin resistance within two weeks, despite a significant lower food intake. The mechanisms of the weight gain implied an increase in the intestinal glucose absorption, energy extraction from non-digestible food

component and a concomitant higher glycemia and insulinemia, two key metabolic factors regulating lipogenesis (Backhed *et al*, 2004).

In addition to this lipogenesis modulation, Backhed *et al*. found that germ free mice had a lower monosaccharide uptake from the intestine to the blood. This last phenomenon could be partly explained by the lower capillary density of the small intestine of germ free subjects as compared to their normal counterparts. The data provided evidence that the digestion of polysaccharides by microbial enzymes and the increased saccharides delivery to the liver, participates to increase lipogenesis. Moreover, the presence of microbiota induces an increase in blood leptin. Lastly and interestingly, germ free mice are protected against obesity induced by a Western-style, high-fat, and sugar-rich diet contrarily to mice with an intestinal microbiota (Backhed *et al*, 2004).

The microbiota of obese human generally has a higher ratio of a particular bacterial phylum and that paradoxically extracts more nutrients than the lean microbiota from an equivalent food bolus. This can contribute a vicious circle of continuous weight gain amongst overweight and obese individuals.

2.6 Exogenous estrogen

“The birth control pill”, or oestro-progestatif therapy, is popular particularly among young women. This therapy brings an excessive consumption of exogenous estrogens. Hormones used in the food industry and soil treatment are a second source of exogenous estrogens (Bacci *et* Leibaschoff, 2006).

Exogenous estrogens are absorbed and enter the body as exogenous substances that cannot be bound to liver proteins and are not recognized by the estrogen pituitary gland feedback mechanism which controls estrogen secretion. Thus, free exogenous estrogens are transported through the vascular system and are generally distributed among the peripheral adipose tissues resulting later in lipogenesis and water retention in the extracellular matrix, while endogenous estrogen secretion is carried on continuously (Bacci *et* Leibaschoff, 2006). Lipogenesis is mainly stimulated by insulin and estrogens. These exogenous estrogens may bring peripheral hype-estogenemia which, when accompanied with hyper-insulinemia, might then become the main cause of peripheral lipidemia observable in areas with a steatomeric structure of adipose tissue, such as hips, abdomen, and flanks in woman and abdomen, flanks and the back in men (Bacci *et* Leibaschoff, 2006).

2.7 Leptin path abnormalities

A few cases of obesity have been linked to leptin resistance. One mechanistic hypothesis is the defective specific leptin receptors in adipocytes. Thus the high levels of leptin noticed in obese individuals do not signal satiety as they should.

2.8 Endocrine malfunctions such as hypothyroid disorder

Endocrine malfunctions such as hypothyroid disorder can influence the development of overweight. Hypothyroidie is characterized by a lack of thyroid hormone, which is a hormone that stimulates the basal metabolism in the way that a person who is resting consumes more energy (Sherwood, 2006). The reduction of the basal metabolism energy consumption can lead to energy storage.

2.9 Psychological and media influence

There is not one specific overweight psychological profile, but quite the contrary, many different psychological states such as depression and stress which can influence weight gain (Houille Lepigeon, 2012). The following paragraphs will explore emotional, cognitive and media influences on dietary habits.

2.9.1 Emotional and psychological factors

Certain psycho-affective factors such as emotions, moods, anxiety, psychological stress, etc. clearly influence eating habits. These can interact in particular with sensorial factors linked to food intake (aspect, odor, taste of foods, etc.). These sensorial factors can obtain an emotional dimension and create or encourage elaborate feelings influencing food intake such as anticipated pleasure, desire, culpability, frustration, and disgust (Houille Lepigeon, 2012).

2.9.2 Cognitive food intake control.

Despite energetic reasons that motivate food intake, eating is a voluntary decision. Everyone is free to eat or not. For example, hunger motivates food intake, the will to lose weight restrains food intake, certain professional obligations delay food intake, etc. We can thereby allow ourselves or prohibit ourselves to eat. However, this cognitive food intake can become surpassed by external and/or psycho-affective factors (the sight of certain foods soliciting emotions such as desire, urge, stress or anxiogenic situations). This is how certain

eating disorders, that can be responsible of important weight anomalies, can emerge (Houille Lepigeon, 2012).

2.9.3 Media influence

2.9.3.1 Sociology and weight loss: body image though out decades

The "ideal woman" in today's society has a large resemblance with a girl at a pre-puberty stage. This observation raises a certain number of concerns for the psychological well being of women today. Indeed when you look at a magazine or a fashion show the models are very often aged less than 18 and have a BMI of someone who is underweight.

Thanks to old sexual education text books dating from the 1800s, Thibault De Saint Po, a sociologist from INSEE, France's National Institute of Statistics and Economic Studies (Institut National de la Statistique et des Études Économiques) noticed the change in the body shape of the ideal men and women through time. These body shapes have enormously evolved in the past 50 years. The texts books show that the ideal body has considerably lost weight, to the point that **the ideal body in 2008 resembled the image describing pathologic thinness in 1848 in France**.

He explains that for a woman today, being thin is like having a supplementary diploma that the work market will financially recognize. Indeed it has been shown that overweight, notably obese, women do shorter studies. They also have more trouble finding a job because the French society tends to have the idea that an overweight woman show signs of carelessness and laziness and that an employer cannot trust her. Thus being thin seems perceived as an asset in French society (Pichon, 2012).

A perfect body is perceived as guarantee of productivity in our occidental consumption based society founded on normalization, notably the current norm that is staying young, svelte and dynamic. Today a person has a commercial value. Someone active who makes decisions represents the image of the young working active. Thus staying young or at least seeming young has become an imperative to remain in the competition (Gassia *et al.*, 2007). In addition, our ideal biological body no longer corresponds with the one given by nature, in other words the body destined to become deformed by work and aging. It has become an object that we can shape as we please. Today everyone receives pressure to become conform to an imaginary ideal, with our society's values and norms dictated by publicity and media. Magazines such as *Elle* and *Cosmopolitan* for women as well as *Men's Health* for men have become guides delivering recipes to obtain an ideal body. These recipes and advice are indexed on collective standards (ideas and dreams) and promote individual will. The

objective is thus to be oneself while paradoxically following rules defined by fashion (Gassia *et al.*, 2007).

2.9.3.2 Men and their body image

The will to stay thin is also progressively affecting men. David Le Breton, a sociology Professor at the university Marc Bloch of Strasbourg studied men in our society today. He noted that beauty requirements affect an increasing number of men who are becoming more and more conscious and concerned by their power of seduction and beauty. They try to remain looking young with a chiseled body. Masculine magazines and cosmetics for men are becoming growingly successful. In addition, men's tendency to follow weight loss diets, to buy thinning cosmetics or to spend time at the gym is also increasing. Indeed beauty is imperative in all societies and it mobilizes women and men of all ages around an increasing attention that plays on self-esteem (Gassia *et al.*,2007).

2.10 Conclusion on causes

To conclude, the main reason for the development of overweight is a positive energy balance between the amounts of energy consumed over the energy spent in everyday life. Indeed, the excessive fat accumulation in adipose tissue leading to obesity is the result of a chronic overconsumption of foods and drinks that is greater than the energy expenditure requirements, in which dietary and lifestyle habits, sociological factors, metabolic and neuroendocrine alterations, hereditary components (Marti *et al.*, 2004) as well as gut microbiota are involved.

3. Possible complications

Overweight and obesity can lead to many complications for an individual including physical repercussions such as co-morbidities, psychological repercussions such as loss of self-esteem, as well as aesthetic consequences such as cellulite or skin alteration.

3.1 Physical repercussions of overweight and obesity

3.1.1 Functional repercussions

3.1.1.1 Co-morbidities

Hippocrates wrote "Corpulence is not only a disease itself, but the harbinger of others", explaining that obesity is a medical disorder that also leads to many co-morbidities.
Substantial literature has found that overweight and obesity are major causes of co-morbidities which can lead to further morbidity and mortality. A meta analysis conducted by

the Centre for Health Evaluation and Outcome Sciences at St Paul's Hospital, in Vancouver on 89 relevant studies revealed that both overweight and obesity are associated with the incidence of multiple **co-morbidities including type II diabetes, cancer and cardiovascular diseases.** They concluded that the maintenance of a healthy weight could be important in the prevention of the large disease burden in the future (Guh *et al.*, 2009).
The morbidity associated obesity and overweight has been associated with co-morbidities, notably the ones cited below.

Common health consequences of overweight and obesity:

- Cardiovascular diseases (mainly heart diseases and stroke) : leading cause of death in 2008
- Hypertension
- Metabolic disease
- Diabetes
- Inflammatory disease
- Musculoskeletal disorders (mainly osteoarthritis)
- Certain cancers

The risk of these diseases increases with the increase in BMI. (Ciangura *et al.*, 2010; Guh, 2009).

In addition, it is well recognized that the distribution of the fatty mass influences the risk of co-morbidities. Accumulation of fatty tissue in the upper part of the body, the so-called **android abdominal adiposity, is associated with an increased vascular and metabolic risk, independently of overall overweight**. The quantity of abdominal visceral fat is the critical element in the genesis of complications (Ciangura *et al*., 2010).

Metabolic syndrome is a significant public health problem worldwide. Both insulin resistance and central obesity are considered to be significant factors contributing to the development of metabolic syndrome.

According to the International Diabetes Federation definition, for a person to be defined as having the **metabolic syndrome** they must have:

• **"Central obesity** (defined as waist circumference ≥ 94cm for European and North American men and ≥ 80cm for European and North American women, with ethnicity specific values for other groups. If BMI is >30kg/m², central obesity can be assumed and waist circumference does not need to be measured)

Plus any two of the following four factors:

• **Raised triglycerides** ≥ 150 mg/dL (1.7 mmol/L) or specific treatment for this lipid abnormality
• **Reduced HDL cholesterol**
< 40 mg/dL (1.03 mmol/L) in males
< 50 mg/dL (1.29 mmol/L) in females
or specific treatment for this lipid abnormality
• **Raised blood pressure (BP)**
systolic BP ≥ 130 or diastolic BP ≥ 85 mm Hg
or treatment of previously diagnosed hypertension
• **Raised fasting plasma glucose (FPG)**
FPG ≥ 100 mg/dL (5.6 mmol/L),
or previously diagnosed type 2 diabetes"

(International Diabetes Federation, 2006)

Although in the past morbidity associated obesity and overweight was clearly associated with economical damage for society, **today research is pointing in the direction that drastic weight loss may be more damaging than remaining overweight.**

3.1.1.2 Other possible complications

Digestive disorders can also be frequent in the case of obesity; they can be linked to heart burn, coughing, esophagitis, gastro-oesophageal reflux, and the risk of ulcers.

Fatigue is often noticed in overweight individuals as well as difficulty to do physical activity linked to the risk of falls, flat feet, the difficulty to get up, breathlessness, etc (Houille, 2012).

The skin of obese individuals can become fragile due to the difficulty of washing linked to the multiple creases, excessive transpiration and maceration that increase the risks of irritative dermatitis and mycoses (Houille, 2012). Overweight or obese individuals can present stretch marks and/or flaccid skin notably due to the alternation of weight gain and weight loss.

Subcutaneous adipose tissue, found directly below the skin, is an important heat insulator in the body, because it conducts heat only one third as much as other tissues. The degree of insulation is dependent upon the thickness of this fat layer. For example, a person with a 2-mm layer of subcutaneous fat will feel as comfortable at 15°C as a person with a 1-mm layer at 16°C. This may explain one of the reasons why overweight can lead to excessive perspiration. Indeed, excessive perspiration is frequently complained about in overweight and obese individuals (Albright *et* Stern, 1998; Houille, 2012).

In addition, an obese person can be at risk when necessitating surgery or anesthesiology because they tend to have weakened wound healing, respiratory troubles, and a higher risk of infection due to diminished immunity system (Houille, 2012).

3.1.2 Esthetic repercussion: Cellulite

Term "cellulitis" is also often inappropriately used by women to describe curves which they judge to be too plump and unaesthetic, mainly around the thighs and hips. It is clinically characterized by a skin surface resembling an "orange peel". This is due to the excessive increased volume of the adipocytes that are organized in lobules within walls of unstretchable conjunctive tissue. Insufficiency of venous tonus and an increase in the capillary permeability, which both contribute to an increase in the infiltration of water in the tissue, can be added to this phenomenon (Franchi *et al.*, 2003).

In medicine, the suffix "itis" refers to inflammation, phlogosis ("inflammation of external parts of the body") (Webster's Revised Unabridged Dictionary, 1913) or infection, thus bringing us to believe that "cellulitis" might refer to inflammation of the cells involved. Cells (along with interstitial structures) integrate the microvascular-tissular unit of all living tissues. In "cellulite", there is no phlogosis of the cells, but most likely an alteration of interstitial tissues. There has thus been an empirical misuse of the medical term in our everyday life, indeed cellulitis is not merely an inflammatory process.

Cellulite is not a serious condition from a medical point of view, but it does represent the most widespread and least tolerated aesthetic complaint among women. However the importance of a purely aesthetic problem should not be underrated especially cellulite since it is the subject of intense publicity campaigns in the mass market which can contribute to the psychological repercussions (Bacci *et* Leibaschoff, 2006).

3.2 Psychological repercussions of overweight and obesity

Being overweight can lead to psychological complications such as a feeling of rejection, stigmatization, social discrimination, etc. It can also lead to the loss of self-esteem, eating disorders, or isolation to only sight a few examples. Someone obese or overweight may find it difficult to accept him or herself as they are.

3.3 Conclusion on the complications of overweight and obesity

Obesity and overweight can lead to many to complications for an individual, both physically and psychologically.

Physical repercussions include co-morbidities such as cardiovascular diseases (mainly heart diseases and stroke), hypertension, metabolic disease, diabetes, inflammatory disease, musculoskeletal disorders (mainly osteoarthritis), as well as aesthetic consequences such as cellulite or skin alteration. Although cellulite is not a serious condition from a medical point of view, it does represent the most widespread and least tolerated aesthetic complaint among women. This brings us to the psychological repercussions that overweight and obese subjects can suffer from, such as loss of self-esteem or social discrimination.

4. Overall conclusion on overweight and obesity

Medias and food industries play an important role in the emergence of psychological repercussions for overweight individuals since they prone being thin and often offer somewhat controversial weight loss strategies (Le Barzic, 2010). Although in the past obesity and overweight were clearly associated with economical damage for society, today research is pointing in the direction that drastic weight loss may be more damaging than remaining overweight. There are numerous factors to take in account when assessing the risk of health damage linked to high adiposity. Indeed, the distribution of the fatty mass influences the risk of co-morbidities. To illustrate, the quantity of abdominal visceral fat is the critical element in the genesis of complications, in comparison with the accumulation of fatty tissue in the lower part of the body (hips and thighs) which is less linked to the genesis of co-morbidities.

The next part of the thesis explains the influence of adipose tissue distribution as well as the histology, origin, and metabolism of adipocytes.

PART 2: ADIPOSE TISSUE

1. Definition of adipose tissue

Adipose tissue is specialized connective tissue. An adipocyte is a metabolically active cell which plays a central role in the control of the body's energy balance. To do so, it possesses all the enzymatic equipment necessary for synthesis (lipogenesis) and for triglyceride storage, mobilization and hydrolysis of free fatty acids (lipolysis). The adipocyte has a central role as an energetic reserve which manages the lipogenesis/lipolysis balance, as well as the status of an endocrine and paracrine cell since it secretes many factors (Franchi *et al.,* 2003).

Adipose tissue is mainly characterized by the presence of a high number of adipose cells forming a tissue with scarce ground reticular substance (Bacci *et* Leibaschoff, 2006). The majority of adipose tissue is a lose association of lipid-filled cells called adipocytes, which are held in a network of collagen fibers. In addition to adipocytes, adipose tissue contains stromal-vascular cells including fibroblastic connective tissue cells, leukocytes, macrophages, and pre-adipocytes (not yet filled with lipids), which contribute to the structural integrity. (Albright *et* Stern, 1998).

There are two main types of fat: Primary and secondary according to the preferential area located, activity and embryological origin.

2. Localizations of body fat

2.1 Adipose tissue classification

Adipose tissue can be classified in three sorts according to its hypodermal, visceral, or peripheral locations. It is mainly located at a subcutaneous level as well as within the muscle interstitium and in the omentum, mesenterium, and peritoneum.

The hypodermis is composed of fundamental substance, fibers and cells. The cells are principally adipocytes. In a normal individual of average weight, 15 to 20 percent of body weight is adipose tissue, which corresponds to 50 to 80 billion adipocytes. The hypodermis is attached to the upper part of the dermis thanks to expansions of collagen fibers and elastic fibers. Its thickness is variable: thin at the forehead, thick at the buttock. (Dubois, 2007 ; Fritsch *et* Kühnel, 2003 ; Melissopoulos *et* Levacher, 1998)

2.2 Android and gynoid body fat distributions

There are clear qualitative and quantitative differences in hypodermis between men and women. For the majority of men, the adipose tissue is mainly located "over the belt", in the abdomen and shoulders. In women adipose tissue is found most commonly "under the belt" in the lower part of the abdomen in the hips, buttock and thigh regions. These locations with the biggest subcutaneous adipose tissue reserves are linked to the person's sex and are a quite marked in the case of obesity. There are two forms of obesity: the android and gynoid type as illustrated in the picture below (Melissopoulos *et* Levacher, 1998; Meynadier, 1980; Dubois, 2007). The android body fat distribution pattern is often compared to an apple shape whereas the gynoid body fat distribution is often compared to a pear shape.

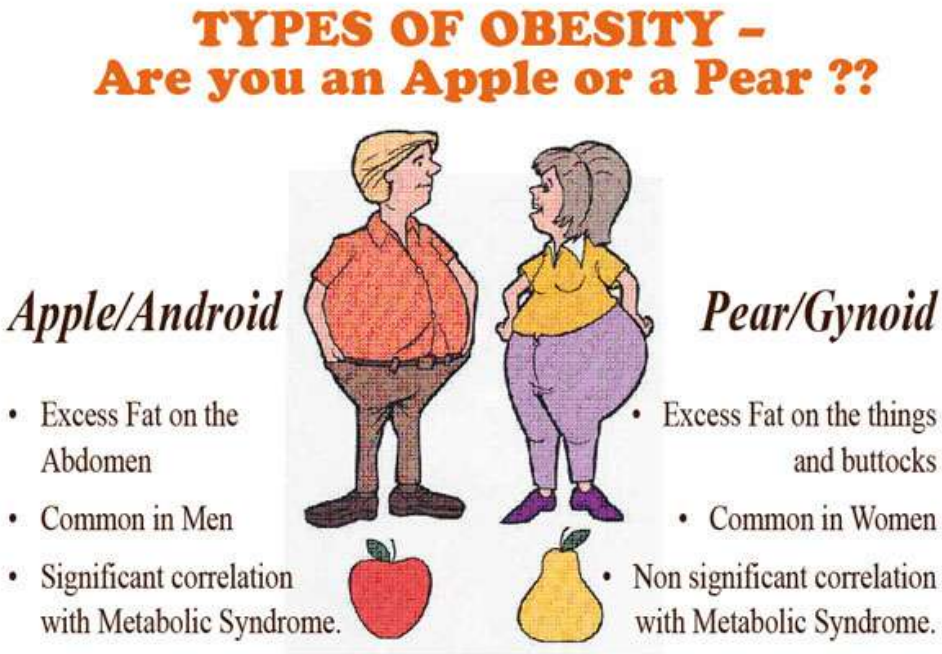


Figure 3: Apple and Pear representation of fat distribution (Berita Perawat, 2010).

This dimorphism of gynoid or android fat distribution emerges quite clearly at puberty. With age (after menopause for women) these differences are less noticeable.

3. Primary fat: brown adipose tissue

Primary fat, also known as brown adipose tissue is a brown colored fat preferentially located in cavities. It is mainly present in animals that hibernate. In humans, the prevalence of brown adipose tissue decreases with age (Bacci *et* Leibaschoff, 2006; Richard et al., 2012).

The brown color of this tissue is derived from the cells' rich vascularization and densely packed mitochondria. Brown adipocytes have a developmental origin that largely differs from that of the white adipocytes. Indeed, they are steatoblastic from an embryological point of view (Bacci *et* Leibaschoff, 2006; Richard et al., 2012).

Brown adipose is a remarkable heat-producing tissue, which is important for regulating body temperature. The lipids in brown adipose tissue, when released as energy, are used directly for heat production also known as thermogenesis. The thermogenic potential is conferred thanks to an uncoupling protein 1 (UCP1), a protein found mainly in brown adipocytes. UCP1 is a mitochondrial inner membrane protein that is capable of uncoupling mitochondrial oxidation from ATP synthesis, in a process that triggers heat production through enhanced cellular respiration. Brown adipose tissue activity and capacity is controlled by the sympathetic nervous system (SNS), which densely innervates brown fat depots (Richard et al., 2012.)

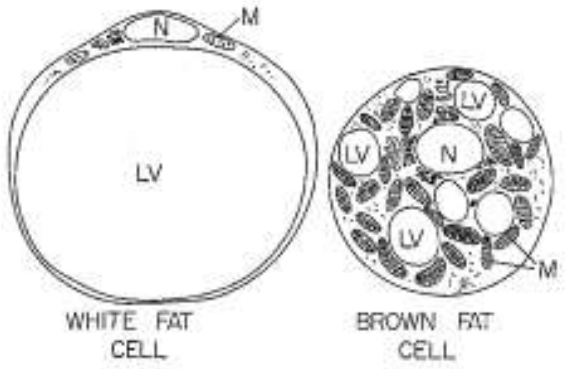


Figure 4: White fat cell and brown fat cell. (Albright *et* Stern, 1998) Notice the single large lipid vacuole in the white fat cell and the numerous smaller lipid vacuoles in the brown fat cell. LV: lipid vacuole; M: mitochondria; N: nucleus

4. Secondary fat: white adipose tissue

Secondary fat is commonly called white fat or white adipose tissue. White adipose tissue has three main functions: heat insulation, mechanical cushion, and most importantly, a source of energy (Albright *et* Stern, 1998). It is the most important energetic storage and consists of almost the totality of our triglyceride stocks. Although it is called white adipose tissue, its color depends on dietary habits and is generally yellowish due to its impregnation with carotenoids and lipochrome pigments (Meynadier, 1980).

5. Histology

The adipocyte is a spherical cell whose cytoplasm is filled with a large vacuole full of triglycerides. This lipid filled vacuole pushes the nucleus and the cytoplasm which become a thin layer (Figure 5).

When observed with an electron microscope, adipocytes show a network of Golgi's corpuscles, mitochondria, and ribosome spread out with in a cytoplasm, which becomes thinner near the central fat drop. The adipose drop has no membrane of its own and proffers filaments that extend to the cell's surface (Bacci *et* Leibaschoff, 2006).

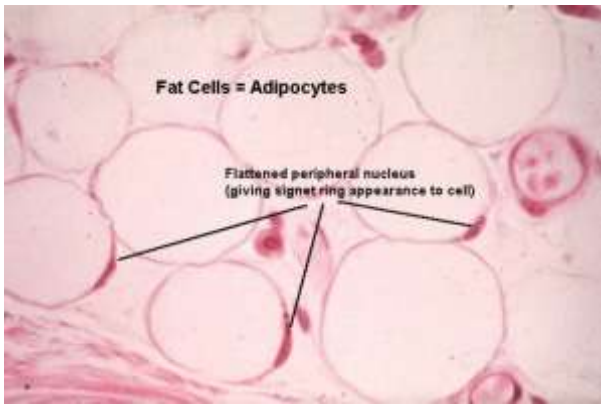


Figure 5: Histological view of the general structure of an adipocyte (Pinna, 2010).

Although each adipocyte in white adipose tissue is in contact with at least one capillary, white adipose tissue is not as richly vascularized as brown adipose tissue. The blood supply provides sufficient support for the active metabolism, which occurs in the thin rim of cytoplasm surrounding the lipid droplet. Blood flow to and from adipose tissue varies depending on the body weight and the nutritional state of the person, with blood flow increasing during fasting (Albright *et* Stern, 1998).

6. Origin

White fat tissue cells derive from normal mesenchimal (mesenchymal) cells. In fact, every fibroblastic cell may be transformed into an adipose cell under specific conditions or body requirements (Bacci *et* Leibaschoff, 2006).

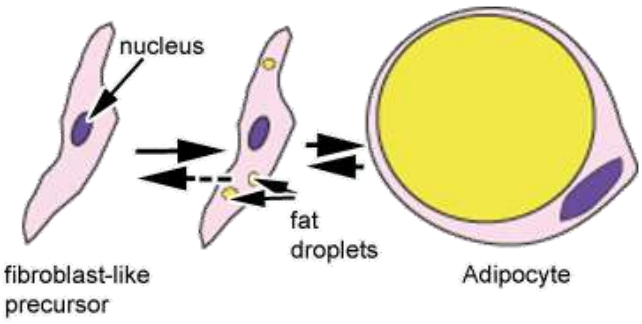


Figure 6: Transformation of a fibroblastic cell into an adipose cell, (Connective Tissue, 2012).

The transformation of pre-adipocytes into adipocytes is promoted by overeating and slowed down by physical activity. This transformation generally takes place during three different periods of life: the last three months of gestation in the case of maternal overfeeding, the first year of life, and preadolescence (Sherwood, 2006).

In addition, when adipocytes fill up with lipids and get to a critical size, precursor cells are stimulated to differentiate, and an **increase in adipocyte number results**. Moderate overfeeding must generally be long term in order to reach this critical size. There are most likely individual differences in the critical size that will result in new adipocyte formation from one person to another (Albright *et* Stern, 1998). It is important to understand that an adipocyte is a differentiated cell and is thus not capable of multiplication. The new adipocytes come from a pre-adipocyte or progenitor cell capable of proliferation and differentiation (Franchi *et al.*, 2003). **Once new adipocytes are formed, they remain throughout life and only a reduction in size of the cell is possible. This increased number of adipocytes has important consequences for the treatment and prevention of obesity** (Albright *et* Stern, 1998).

7. Role

The primary **roles of adipose tissue are to insulate and cushion the body as well as to store free fatty acids** (FFAs) after food intake and to release FFAs throughout a human's life (Hajer *et al.*, 2008). Indeed the hypoderm constitutes the largest energetic reserve in the organism.

Adipose tissue is classically perceived as being solely a storage place for fatty acids. Today research has shown other functions such as a role in lipid and glucose metabolism as well as cytokine production (Bacci *et* Leibaschoff, 2006).

Next the adipocyte fat storage and energy release will be explored.

7.1 Lipid and glucose metabolism

7.1.1 Lipid storage

After a meal, the adipose tissue can accumulate lipids under the form of triglycerides for energy storage. This is called lipogenesis (Girard, 2011).

During digestion, lipids pass through enterocytes into the blood circulation thanks to different enzymes (Melissopoulos *et* Levacher, 1998) as we will see further in the thesis. Adipocytes synthesize a particular enzyme: the lipoprotein lipase (LPL). The LPL transforms triglycerides, contained in lipoproteins (very low density lipoprotein: VLDL), into free fatty

acids (FFA) and glycerol, in the blood vessels (Hajer *et al.*, 2008). The schematic structure of a triglyceride is shown below (fig. 7).

Figure 7: Schematic structure of a triglyceride (Fatty acid metabolism, 2012).

The FFAs liberated into the blood stream can then either be used immediately or stored in the adipocytes. When they are stored, the FFAs penetrate the adipocyte due to a concentration gradient. The figures below are schematic representations of the following steps (fig. 8 and 9).

1) After food intake dietary lipids enter the intestine.

2) The lipids are degraded by a pancreatic lipase liberating FFAs.

3) The FFAs pass into the intestinal cell.

4) The FFAs are reassembled into triglycerides then packed into chylomicrons inside of the intestinal cell and lastly secreted into the blood stream.

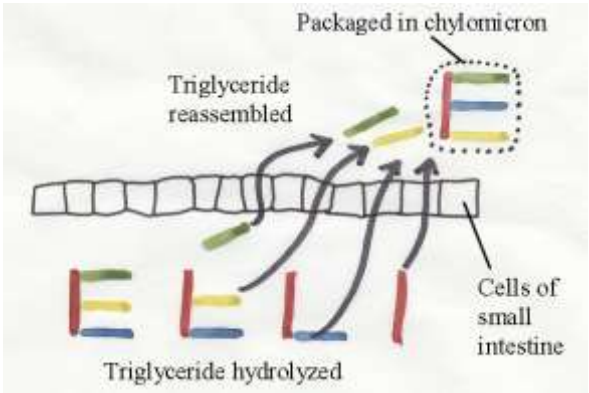


Figure 8: Uptake of dietary lipids through the intestinal barrier (Fatty acid metabolism, 2012).

5) The TGs in chylomicrons (if they are from a dietary source) or in VLDLs (if they are from an endogen hepatic source) are hydrolyzed by the LPL, liberating FFAs.

6) The FFAs are uptaken by the adipocyte.

7) Once in the cell, glycerol from the glucose metabolism participates to the synthesis of TG (Melissopoulos *et* Levacher, 1998). Indeed, plasmatic glucose is also captured by the adipocyte thanks to specific receptors (figure 9).

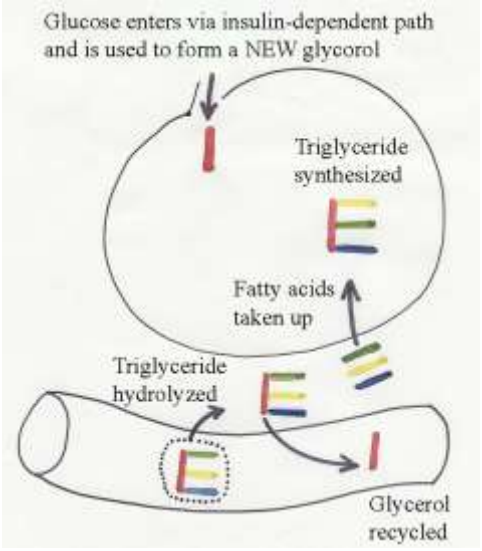


Figure 9: Triglycerides uptake and storage is dependant of specific receptors and promoted by insulin(Fatty acid metabolism, 2012).

Energy ingested as lipids above what is needed for energy demands is stored in adipose tissue. The storage of fatty acids in the adipocyte is associated with an increase in adipocyte size. Carbohydrates and proteins consumed in the diet can be converted to fat in the form of FFAs. Energy ingested as carbohydrates are generally stored as glycogen in the liver and muscle but can also be converted to triglycerides primarily in the liver and transferred to adipose tissue for storage. Amino acids from ingested proteins are used for new protein synthesis or certain can be converted to carbohydrate and fat (Albright *et* Stern, 1998).

Next this thesis will explore the mobilization of FFAs stored in adipose tissue.

7.1.2 Lipolysis

Contrarily to lipogenesis, in fasting periods, the adipose tissue mobilizes the energy needed by the body. This is called lipolysis (Girard, 2011; Melissopoulos *et* Levacher, 1998). Lipolysis mainly takes place when energy or thermoregulation is needed. It is characterized by the outflow of circulating fatty acids from the adipose tissue (Bacci *et* Leibaschoff, 2006). The reserve of FFAs, constituted during the postprandial phase in adipose tissue, is mobilized thanks to the action of the hormone sensitive lipase (HSL) by hydrolyzing the adipocyte TGs (Hajer *et al.*, 2008). Indeed, when the body needs energy, the adipocyte can hydrolyze triglycerides into fatty acids and glycerol. The glycerol is captured by the liver which metabolizes it into glucose (neoglucogenesis) (Melissopoulos *et* Levacher, 1998 ; Kierszenbaum, 2006).

7.1.3 Regulation

The regulation of adipose tissue varies according to body areas and is mainly dependant of sexual hormones (Bacci *et* Leibaschoff, 2006). Both lipolytic and lipogenic hormones are involved in fat metabolism. The **most important lipolytic hormones are thyroid-stimulating hormone (THS), adrenalin, glucagon, somatotrophin, adrenocorticotropic hormone (ACTH), and thyroid hormones. The lipogenic hormones are mainly represented by insulin and estrogens** (Bacci *et* Leibaschoff, 2006).

As mentioned above, when the body needs energy, the adipocyte can hydrolyze triglycerides into fatty acids and glycerol. The enzyme responsible for this metabolism is the triacylglycerol- lipase named HSL or Hormone Sensitive Lipase.

When lipolysis is superior to lipogenesis an overstorage of fatty acids takes place, leading to the multiplication of glucose transporters (GLUT 4), an increase in adipocyte size, and an increase in the number of adipocytes (Cottin, 2011). It is essentially insulin that inhibits lipolysis. Insulin thus has a lipolytic effect (Melissopoulos *et* Levacher, 1998 ; Kierszenbaum, 2006).

7.1.3.1 Insulin

Insulin is a hormone secreted by the beta cells of the pancreas. It plays a predominant role in the regulation of the adipose fat content. Insulin's main role is to enhance storage and block the mobilization and oxidation of fatty acids. Insulin stimulates LPL formation so that circulating triglycerides are hydrolyzed and free fatty acids can enter the adipocyte. Insulin is also required for the transportation of glucose, which is needed for the re-esterification of triglycerides once inside the adipocyte. Finally, the conversion of glucose into to fatty acids is accomplished by insulin's activation of several enzymes (Albright *et* Stern, 1998; Hajer*et al.*, 2008).

The following paragraph concerns the influence of adipose tissues' localizations on their adipocyte metabolism.

7.1.3.2 Influence of adipose tissue localization.

Not all localizations of fatty tissue have the same intrinsic capacity to stock and mobilize triglycerides. Indeed, gynoid adipose tissue (mainly in the femoral subcutaneous region) has been shown to have a higher triglyceride storage and redistribution capacity than adipose tissue in android localizations (deep and subcutaneous abdominal tissue). This is due to the fact that adipocytes in the subcutaneous femoral region seem better equipped for the

capture and storage of triglycerides. Those in the abdominal region are better equipped for their mobilization. The adipocytes in the femoral region have a higher lipoprotein lipase activity (which will be seen below when the influence of sexual hormones will be treated). They also have more numerous insulin receptors than the adipocytes in the abdominal region (Melissopoulos *et* Levacher, 1998).

7.1.3.3 Sexual hormone influence

The fact that cellulite appears in women at puberty and during pregnancy brings us to believe that female sexual hormones (estrogens and progesterone) play an important role in the anatomic distribution of adipose tissue (Franchi *et al.*, 2003).

Similarly, it was observed that premenopausal and menopausal women mainly develop android obesity. During these periods it is known that women are characterized by an imbalance in their estrogen on androgen levels, with the active form of androgens being predominant compared to estrogen. In addition, adipose tissue presents receptors for steroid hormones: the androgen receptors are predominant in the abdominal region while estrogen receptors are predominant in the subcutaneous femoral region (Melissopoulos *et* Levacher, 1998).

As for lipolysis, the abdominal tissue seems more sensitive to sexual hormones. Estrogens seem to potentiate the β-adrenergic effects and thus promoting lipolysis. Contrarily, androgens stimulate preferentially α2-adrenergic receptors which promote lipogenesis. These observations bring a certain explanation as to the development of adipose tissue in women and men (Melissopoulos *et* Levacher, 1998).

7.1.3.4 Other general influences

Lipolysis is generated by nervous and endocrine stimuli, but also by an increase in blood flow. Hence, a blood flow decrease inhibits lipolysis and the outflow of FFA and glycerol (Bacci *et* Leibaschoff, 2006).

7.2 Hormone and cytokine production

Adipose tissue produces a wide range of hormones, enzymes and cytokines that are involved in glucose metabolism (for example adiponectin, resistin), lipid metabolism (for example cholesteryl ester transfer protein, CETP), inflammation (for example TNF-α, IL-6), coagulation (PAI-1), blood pressure (e.g. anginotensinogen, anginotensin II) and feeding behavior (leptin) thus affecting metabolism and function of many organs and tissues including muscle liver,

vasculature, and brain (Hajer*et al.*, 2008). In general, plasma adipocytokin levels rise with an increase in adipose tissue and adipocytes volume, except for plasma adiponectin which is lower in obesity (Hajer *et al.*, 2008).

In the next paragraphs, the roles of leptin, ghrelin and of inflammation will be discussed.

7.2.1 Leptin

Leptin is a protein hormone. It is mainly produced by adipocytes of the white adipose tissue and provides feedback to the brain (in the hypothalamus center) regarding fat mass, especially subcutaneous body fat (Das, 2010; Carnell et al., 2012). Indeed, its production is increased in large adipocytes, stimulated by insulin and affected by TNF-α, estrogens, FFAs, and growth hormone but is not directly influenced by food uptake itself (Hajeret al., 2008). Leptin acts on the hypothalamus and other areas in the brain, stimulates the enzymes involved in lipid metabolism, reduces feeding, and increases energy expenditure (Das, 2010). Leptin acts also centrally to increase insulin's action in the liver (Das, 2010).

The circulating level of the anorexigenic hormone leptin is increased in obese subjects whereas surprisingly, the level of the orexigenic hormone ghrelin is decreased. It is now established that most obese patients are leptin-resistant (Klok *et al.*, 2006).

7.2.2 Ghrelin

Ghrelin is a gut hormone that increases food intake. It is mainly secreted in the stomach. Ghrelin increases hunger through its action on hypothalamic feeding centers which is in turn associated with an increased body weight gain. Blood concentrations of ghrelin are lowest shortly after consumption of a meal, then rise during the fast just before the next meal. Ghrelin has been shown to increase the glucose utilization rate of adipose tissue in fasting conditions in order to control blood glucose levels. In addition, binge-eating has been related to a dysfunction in the ghrelin signaling system (Das, 2010; Hellstrom *et al*., 2004).

Factors that regulate ghrelin secretion and action include plasma glucose, insulin, acetylcholine levels in the brain, leptin, BDNF, and various other neurotransmitters and peptides (Das, 2010).

7.2.3 Inflammation

Evidence indicates that chronic diseases, such as cardiovascular disease and obesity, are part of a group of conditions linked by inflammatory deregulation (Myers *et* Allen, 2011). Indeed, the link between inflammation and obesity was shown in the beginning of the years 2000 by

the observation that the number of macrophages increased in the visceral adipose tissue of obese subjects.

One explanation for the association between obesity and inflammatory deregulation is that the Western diet is obesogenic and promotes the secretion of inflammatory biochemical signals (Myers *et* Allen, 2011). Indeed, high fat and saturated fat diets also promote low grade inflammation which accounts for low-grade systemic inflammation and insulin resistance seen in obesity whereas poly-unsaturated fatty acids (ex. Omega 3 or 6 fatty acids) have anti-inflammatory properties (Das, 2010).

Weight gain results in lipid accumulation and adipocyte stress— factors known to disrupt the balance of systemic cell signaling (adipokines and cytokines) which favors inflammation (Myers*et* Allen, 2011).

7.3.4 Pro-inflammatory markers

The presence of an inflammatory response can be determined by the measurement of the serum concentration of both pro-inflammatory and anti-inflammatory biochemical signals. Pro-inflammatory markers commonly tested include, and are not limited to, C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α), and interleukin 18 (IL-18) (Myers *et* Allen, 2011).

CRP is the first marker to be synthesized in the liver as a response to an inflammatory stimulus. Obesity-induced adipose tissue inflammation is associated with an increased expression of **IL-6**, IL-18, and **TNF-α**, which are synthesized by both macrophages and adipocytes. Adiponectin, is an anti-inflammatory adipokine which is released exclusively by adipocytes and regulates insulin sensitivity; however, its concentration decreases with obesity (Myers *et* Allen, 2011).

8. Conclusion on adipose tissue

Adipose tissue is mainly composed of lipid filled cells called adipocytes as well as fibroblastic connective tissue, leukocytes and macrophages. Adipocytes derive from preadipocytes. There are two main types of fat, white (the large majority in adult humans) and brown adipose tissue. The location of adipose tissue conditions its role and its influence on the body. Indeed abdominal obesity is linked to a higher risk of many diseases than is fat situated “below the belt” in the hips and thighs. Fat can be stored or mobilized according to the body’s needs. Food intake, lipogenesis and lipolysis are under the influence of numerous factors such as insulin, leptin and grelin.

In the next part of this thesis, different non-prescription weight loss strategies will be explored.

PART 3: NON-PRESCRIPTION WEIGHT LOSS STRATEGIES

In this part of the thesis, a certain number of non-medical and non interventional weight loss concepts will be explored. The goal is mainly to clarify the most well-known weight loss methods that are available to the general population without a medical prescription. This is why prescription medication and surgery will not be covered. There are many more weight loss methods that those mentioned in this thesis. The methods which will be explored in more detail are those that came up most frequently during a quick inquiry conducted in the general population. What generally came up first is eating less and healthier as well as exercising. Then, when asked about specific diets, the Dukan diet and Weight Watcher diet came up most frequently. Lastly certain people, mainly women, also mentioned dietary supplements, which will be explored in part 4.

This section of the thesis will explore the motivations and marketing strategies behind the weight loss market, followed by an explanation of the Dukan diet which is extremely well know and common in France as well as the Weight Watchers diet which has been scientifically proven to be effective. Lastly the risks of drastic weight loss as well as WHO recommendations will be explored.

1. Introduction: problematic and weight management market

1.1 Main motivations to follow a diet

According to the survey conducted by GSK Healthcare 2011, the main motivations to lose weight are to live longer for men (43%) and to regain self-confidence for women (58%) other possible motivations to follow a diet are listed below (Girard, 2011; Pichon, 2012):

- To appreciate one's self physically
- Pressure from public health and governmental authorities «The less you are overweight the less you cost us»
- Pressure from the weight loss industry whose interest is to amplify the market

- Pressure from press: most magazines talk about weight loss or dieting in their different editions (which wasn't the case 20 years ago)
- To be in better health (for example to obtain a lower blood cholesterol level or reduce back, knee, or general joint pain)
- To reduce the orange peel effect of cellulite or to lose centimeters in adipose tissue storage zones
- Social pressure, the importance society gives to being thin and self-image (in our society physical appearance is very important).

In the next paragraphs the role of marketing and social pressure to be thin will be explored more in depth.

1.2 Marketing behind weight loss products in France

1.2.1 Driving forces for the weight management market

The driving forces identified for the weight management market are an aging population, a growing number of overweight or obese subjects, an increase in global income levels, an increase in the number of people becoming more health and fitness conscious (increasing the trend of consumption of weight management products and services) and profits driven by growth in the weight management products and services markets. In addition, an increasing desire of the young and rich population to 'look good' from the society's general point of view is also one of the major drivers for the market (PR Newswire Europe; 2012).

Thibault De Saint Po, a sociologist from INSEE, observed that today marketing plays on the fear of an obesity epidemic. Particularly in France, marketers put forward the fact that obesity hasn't affected the French population as much as it has in other countries such as the United States. Marketers illustrate this idea and increase fear of the epidemic by using impressive numbers, for example the cost of obesity. The cost of obesity can easily be contested because it is very complicated to calculate and the figures communicated are out of date which makes the estimations even more contestable. Another example is the prevalence of overweight and obesity. These figures tend to be added together in order to obtain alarming sums. For example with children if you add the numbers of overweight and obesity you get 15 to 18 percent instead of the 3 percent of obese children in France (Pichon, 2012).

George Lewi, Marketing Professor at HEC Paris and CELSA, observed that when a nutritionist consults and prescribes, this act can be considered as giving advice, personal care or him sharing his knowledge, experience and expertise. When a nutritionist writes a book this too can be considered as above. But when there is a brand extension, in other words, under the same brand name there is no longer personal advice but advice given on internet automatically or that there are products sold, then the diet method belongs to the marketing branch rather than to the personal care branch because indeed the main intention of brands and marketing is to sell more. It is thus a market that surfs on the public health sector (Pichon, 2012). Yet, these methods are becoming more and more popular. The two dieting methods that will be described further in this thesis, the Dukan diet and Weight Watchers diet now offer these services. The Dukan diet will be explored due to its popularity in France and the Weight Watchers diet because it is the only diet which has been backed by scientific proof and has scientific evidence of its effectiveness.

The weight loss business seems to be composed of two main elements: The fact that not being overweight is good for one's health, which is objective, and the notion of desire and pleasure, which is subjective. The combination of these two elements gives a winning marketing strategy (Pichon, 2012) which can be easily illustrated by the quickly increasing figures of the weight loss market as will be explained below.

1.2.2 Value and growth of the weight management market

George Lewi also explains that today if we group together the figures it can be considered that the weight loss market accounts for about 500 million Euros in France, which is a considerable market size for weight loss products and methods. To that must be added books and peripheral products such a certain foods promoted in certain dieting methods, whose sales have been strongly reinforced due to the population's interest in weight loss; the total being of about 1,5 billion Euros today in France (Pichon, 2012). According to a new report published by Transparency Market Research in 2012, Europe's weight management market was estimated to be of 139.5 billion USD in 2011 and is expected to reach 216.1 billion USD in 2015. The food (diet) and beverages segment accounted for the largest share at 36.1% of the European weight management market in 2011. Weight management services are forecasted to be the fastest growing segment with a 13.7% increase between 2011 to 2015 and are expected to reach 66.4 billion USD in 2015 (PR Newswire Europe, 2012); this reveals excellent potential in terms of value and growth for the weight management service companies. This observation may explain the propelled development of internet coaching and methods such a as the Weight Watchers diet method of group coaching.

2. Exercise

The more we exercise the more calories we burn each day. There is an important increase in energy expenditure during exercise. Fat-free mass represents a key determinant of the magnitude of the resting metabolic rate (Xiao *et* Yang, 2012). The more muscle we have, the more the body consumes calories even when resting.

Weight loss can induce a decrease in lean tissue which will decrease the resting metabolic rate. The best way to bring the resting metabolic rate back up increasing muscle mass by doing regular physical activity (Binnert *et* Tappy, 2001) such as aerobics, cycling, or jogging for approximately 30 min/day or more moderate activity for 60 to 75 min/day.

In addition, studies have shown that moderate endurance exercise, such as brisk walking for 45 to 60 minutes, 4 times a week, generally induces only minor weight loss in 1 year when done alone without dietary measures (Heymsfield *et al.*, 2011; Xiao *et* Yang, 2012). Thus, in addition to an exercise program, lifestyle measures as part of a comprehensive weight loss program should always be prescribed (Heymsfield *et al.*, 2011). In the next paragraphs two dieting methods will be described.

3. Two common commercial weight loss diets

In 2010 one out of three people in France followed a diet (Pichon, 2012). Because obesity and overweight mainly result from an imbalance between energy intake and energy expenditure, decreased energy intake is generally required for successful weight loss. The following paragraphs will detail two well-known dieting methods, available without medical surveillance, in France. Their different characteristics will be explored.

3.1 The Dukan diet

3.1.1 General presentation and concept of the method

The Dukan diet was created by Doctor Pierre Dukan who is a French nutritionist. His first book is a best-seller named "Je ne sais pas maigrir" which can be translated as “I don’t know how to lose weight”. It came out in France in 2000. Since then he has written other books and claims having sold 4 million books in France and about 4.5 million in the rest of the world. According to the French documentary “Regimes… Un marché en surpoids” which could be translated as “Diets, an overweight market”, by Sunset Presse, broadcasted on March 22nd 2012 on French television, there are **25 million adepts of his diet in the world**. Doctor Dukan no longer gives personal consultations, instead his method offers internet

coaching with the possibility to send questions by email, for about 1 to 2 Euros per week (Pichon, 2012).

The Dukan diet is divided into 4 phases as described below.

Phase 1, called the **attack** phase, is a strict lean protein diet. It lasts an average of 5 days in order to achieve quick weight loss. It is very strict as only a list of 72 reasonably low-fat protein-rich foods, such as chicken, turkey, eggs, fish and fat-free dairy are authorized. This phase offers a hyperprotein ketogenic diet bringing about 50 percent of the recommended nutritional intake. The production of ketones is mainly due to cutting out carbohydrates form the diet. This phase causes rapid weight loss and puts the body in starvation mode which inevitably has important consequences, both short term (dizziness, bad breath, etc.) and long term (renal problems, rebound weight regain when carbohydrates are eaten, etc.)

Phase 2 is known as the **cruise** phase. It consists in alternating days where the client eats exclusively proteins and days where the client eats proteins associated with vegetables (28 vegetables are allowed). Many foods are prohibited, such as carbohydrates, wholegrains, fruits, sweets and certain vegetables containing sugars. This second phase is meant to lead to the weight objective identified by the client. It lasts about one week per kilogram lost until the weight loss goal has been obtained.

Phase 3 is called the **consolidation** phase. This third phase lasts 10 days per kg lost and is meant to prepare the return to a balanced diet. During this phase, clients are allowed to eat the proteins of the attack phase and the vegetables allowed in the cruise phase as well as one portion of fruit, 2 slices of whole wheat bread, 40 grams of cheese, 2 table spoons of oat bran and 25 minutes of walking per day. Two portions of carbohydrates per week, as well as pork, lamb and 2 festive meals per week are also allowed. This monitored freedom aims to avoid quick weight regain during the introduction of previously unauthorized foods.

The last phase is a definitive phase, in other words a lifelong **stabilization** phase. Each day three spoonfuls of oat bran should be consumed as well as one day per week of the attack phase diet. Oat bran is rich in soluble fibers which help moderate appetite which increases the feeling of satiety and limits the absorption of fats and sugars. This phase is both the least strict and most essential in the slimming method because 95% of people who follow a diet put back on the weight they have lost (Dukan Diet Official Site, 2013; Houille Lepigeon, 2011; Pichon, 2012).

Figure 10: The four phases of the Dukan diet (Dukan Diet Official Site, 2013).

The Dukan diet is poor in lipids (slightly inferior to recommended nutritional intake), poor in carbohydrates (11 to 19% of the recommended nutritional intake) and non hypocaloric (1800 Kcal/day on average).

3.1.2 Pros

This type of weight loss diet should be recommended mainly to people necessitating substantial weight loss (BMI above 27).

It is a very strict diet which some people like.

Weight loss can be very quick the first week: 4 to 5 kilograms then can slow down to attain 8 to 12 kilograms lost in a month. The quick drop in weight can be motivating.

The weight lost consists in over 80% of adipose tissue, the rest consisting in fat-free mass.
The more the dietary habits are changed during the different phases of reintroduction of foods, the more weight loss is stabilized in the long run.

The diet is easy to follow. Food does not need to be weighed nor calories counted. Apart from keeping to low-fat, low-salt and high-protein foods, there are no restrictions as to how much you can eat during your first two weeks as long as you only eat the authorized foods.

The hunger sensation is lessened 48 hours after the beginning of the diet due to the production of ketones (Dukan Diet Official Site, 2013; Houille Lepigeon, 2011 ; NHS choices, 2011;Pichon, 2012).

3.1.3 Cons

The diet is easy to follow but very restrictive which can lead certain people to abandon the diet, often leading to rebound weight regain.

There are many side effects, generally transients and at the start of the diet. Many are due to the production of ketones. The possible side effects include:

-Insomnia, tiredness, dizziness
-Nausea, vomiting, diarrhea, abdominal pain
-Constipation, hemorrhoids (which can be due to lack of wholegrains, fruit and vegetables)
-Cholelithiasis
-Gout flare, hyperuricemia, renal colic
-Orthostatic hypotension linked to urinary loss of water and sodium.
-Hypoglycemia
-Hair loss and dry skin due to the lack of essential fatty acids
-Feeling cold
-Head aches, difficulties concentrating
-Muscular cramps
-Bad breath due to the elimination of ketones through the pulmonary route (Dukan Diet Official Site, 2013 ; Houille Lepigeon, 2011 ; NHS choices , 2011; Pichon, 2012).

Some of these side effects can impose the abandonment of the diet for medical reasons. An uncomfortable long term effect is the necessity to continue doing days of pure protein once a week for the rest of one's life. It is necessary to drink large quantities of water due to the large protein intake which can be damaging for the kidneys. A hidden side effect can be the need to restrict carbohydrate intake for years after the end of the diet in order to avoid a rebound weight regain since carbohydrate consumption can often lead to rapid weight gain after the diet. Indeed, the body and adipose tissue seems to have a memory of the "starvation period" and seek to stock fat in prevention of a future carbohydrate starvation period (as was done during the Dukan diet). Most people regain at least what they lost during the years following the initial diet.

3.1.4 Conclusion

Rapid weight loss may be motivating at first but it is unsustainable and unhealthy. The Dukan diet lacks variety in the initial phases and there's a risk of getting bored quickly and giving up, inducing rapid weight regain. In addition, the diet is not nutritionally balanced, which is also proven by the fact that vitamin, mineral and fiber supplementation is needed (Houille Lepigeon, 2011 ; NHS choices , 2011). This type of diet could potentially increase the risk of long-term health problems. Indeed, the body is put into starvation mode and produces ketone bodies (a by-product of incomplete fat metabolism). In unusual metabolic circumstances, the brain can use ketones when they are present in sufficiently high quantities, but the long term effects for health are questionable (Albright et Stern, 1998).

The benefit risk balance of this diet should be taken into account considering that the side effects are important.

Again, this type of weight loss diet should be recommended to people necessitating substantial weight loss only if it is followed by a medical professional and only after having tried losing weight through healthy dietary measures and by increasing their physical activity level. Lastly it should be noted that the Dukan diet does not teach people how to eat healthier, it only enables rapid weight loss which isn't necessarily sustainable in the long run.

3.2 The Weight Watchers diet

3.2.1 General presentation and concept of the method

Weight Watchers weight loss strategy has been the same since its creation 50 years ago. The method is essentially based on weekly group support gatherings of people who want to lose weight as well as a point system to count the calories consumed per day with a maximum daily and weekly allowance. These meetings help to reinforce motivation and the goal is to relearn how to eat healthy. Each week in France there are 1200 meetings and 120 thousand adherents.

Weekly menus are offered to help with compliance to the method. Nutritional information is also given by the Weight Watchers host at each meeting. As soon as the fifth week, an exercise plan must be adapted to the physical aptitudes of each person. It is also possible to follow this diet at home, without any particular meetings. Once the weight loss objective has been obtained, a stabilization plan is offered and more points are authorized for each meal in the different menus.

The diet is based on a point system with a unit based on the quantity of energy available in the body once the food has been transformed. This system no longer necessitates the weighing of food, which was done in the past and lead to the abandon of the method due to lack of time. Each food is worth a certain number of points and a daily quota is authorized according to each individual (height, weight, age, sex). As an example, an ice cream cone is worth four points and a small bunch of grapes is worth one point. The number of points per menu increases little by little.

The diet recommends eating on a daily basis 200 grams of fruit, 300 grams of vegetables, 2 to 3 dairy products, to drink 1,5 liters of water, and 2 table spoons of vegetable oil. It also recommends consuming everyday carbohydrates at 2 meals at least, proteins at least at one meal, and to do at least 30 minutes of physical activity per day.

Weight loss is mainly based on support and motivation thanks to weekly meetings, conferences on nutrition, healthy eating, and physical activity. This diet is hypocaloric (1200 to 1500 Kcal/day), hypolipidic (25% of total energy intake), slightly hyperprotein (20% of total energy intake) and normal in terms of carbohydrates (55% of total energy intake) (Collectif, 1999; Collectif, 2004; Houille Lepigeon, 2011; Pichon, 2012).

3.2.2 Pros

The psychological support helps to obtain a better understanding of one's self and a better weight loss efficiency.

No foods are banned thus clients can eat and drink what they want providing that they stick to their points allowance.

The method teaches how to buy, cook and eat healthy and balanced meals. It gives good dietary habits during the weight loss period and for after the weight loss program, thus decreasing the risk of rebound weight regain (Collectif, 1999; Collectif, 2004; Houille Lepigeon, 2011; NHS choices, 2011; Pichon, 2012).

3.2.3 Cons

This method is voluntarily non-medicalized. Each person must pay in order to participate, without the possibility to be reimbursed by social security and must manage his or her weight loss from a medical point of view.

At the beginning, working out the points system may seem just as time-consuming as simply counting calories.

Some people feel pressured into buying Weight Watchers branded foods (though it is in no way mandatory in order to obtain successful results).

Clients must be available in terms of time in order to follow this method.

3.2.4 Conclusion

The point counting system seems to be well balanced and can be a foundation for long-term changes in dietary habits. The method encourages cooking and offers recipes. The support group approach can help keep people motivated and educated about healthy eating (NHS choices, 2011). The fact that the method costs money can be a motivation factor for those

who can afford it, but also can restrict the access to people with limited budgets. Altogether the method seems healthy and positive in the long run for health and dietary education.

4. Risks of different weight loss methods by ANSES (L'Agence National pour la Sécurité Sanitaire)

Results show that all diets can have important side effects and that they are often ineffective. The simple act of losing weight can have consequences no matter which type of method is used.

The main risks of losing weight include:

- Loss of muscle mass
- Loss of bone mass
- Risk for liver and kidneys
- Psychological and behavioral risks (loss of self-esteem because of a failure to lose weight for example. In 80 percent of cases people regain weight in the year following their diet and almost every one regains all the weight lost if not more in the following 5 years).

Continual and diverse dieting without medical surveillance can lead to important complications in the long run such as hepatic inflammation, subtle death, increase in organic pollutants liberated in the body which have consequences such as the disruption of endocrine, reproductive, and immune systems, as well as metabolic dysfunctions which could contribute to weight regain and to the development of health problems. Although ANSES confirms that it has never been proven that intentional weigh loss in healthy subjects reduces cardiovascular mortality, it has been shown in other publications that reducing overweight leads to the reduction of cardio fatigue.

This report was not taken into consideration by Doctor Dukan who contested its content. Weight Watchers on the other hand responded to ANSES's conclusions with a new slogan "Stop dieting and join us!". Weight Watchers considers that they offer a completely balanced food program and is very satisfied with the ANSES conclusions.

In addition ANSES considers that a weight loss diet must be individualized. It thus needs to be adapted to each person's life style, health back ground, etc. (Pichon, 2012). Unfortunately, many doctors are insufficiently trained or have insufficient time to support their patients in their weight loss approaches. Indeed, medical surveillance of each diet seems logistically

complicated. When only slightly overweight, it seems more favorable to seek to stabilize one's weight and work on the acceptance of one's body image rather than looking to lose weight by any means.

5. WHO recommendations

To ensure a healthy lifestyle, WHO recommends eating lots of fruits and vegetables, reducing fat, sugar and salt intake as well as exercising. Based on height and weight, people can check their body mass index (BMI) to see if they are overweight. There are easily available series of publications to promote and support healthy lifestyles that WHO provides on internet. Amongst them are the following easy to understand tips on how to eat healthier (WHO, 2012 c).

12 steps to healthy eating

- "Eat a nutritious diet based on a variety of foods originating mainly from plants, rather than animals.
- Eat bread, grains, pasta, rice or potatoes several times per day.
- Eat a variety of vegetables and fruits, preferably fresh and local, several times per day (at least 400 g per day).
- Maintain body weight between the recommended limits (a BMI of 18.5–25) by taking moderate levels of physical activity, preferably daily.
- Control fat intake (not more than 30% of daily energy) and replace most saturated fats with unsaturated vegetable oils or soft margarines.
- Replace fatty meat and meat products with beans, legumes, lentils, fish, poultry or lean meat.
- Use milk and dairy products (yoghurt, cheese, etc.) that are low in both fat and salt.
- Select foods that are low in sugar, and eat refined sugar sparingly, limiting the frequency of sugary drinks and sweets.
- Choose a low-salt diet. Total salt intake should not be more than one teaspoon (6 g) per day, including the salt in bread and processed, cured and preserved foods. (Salt iodization should be universal where iodine deficiency is endemic.)
- If alcohol is consumed, limit intake to no more than 2 drinks (each containing 10 g of alcohol) per day.

- Prepare food in a safe and hygienic way. Steam, bake, boil or microwave to help reduce the amount of added fat.
- Promote exclusive breastfeeding up to 6 months, and the introduction of safe and adequate complementary foods from the age of about 6 months. Promote the continuation of breastfeeding during the first years of life. " (WHO, 2012 c)

6. Conclusion on non medical weight loss strategies

The major goals in dietary treatments are not only limited to weight loss, but also to an improvement in the quality of life. Modification of risk factors associated to comorbidities, personal satisfaction and trying to establish healthy life habits are also important. To conclude on this section treating different weight loss approaches, it can be said that weight loss is a serious matter and medical surveillance should always be looked for when losing a large percent of body weight. An adapted physical activity program should always accompany dietary measures in order to reinforce the muscle mass and bring up the basal metabolism rate.

The short and long term effects of different diets should be looked at before choosing one, both in terms of possible side effects and in terms of rebound weight regain since putting weight back on after a diet can be discouraging and decrease self-esteem. In some cases of moderate overweight in healthy subjects it can be recommended to stabilize present weight rather than looking to lose weight.

The following and last part of the thesis is mainly intended to help the pharmacist and slightly overweight subjects. It studies active ingredients often found in weight management dietary supplements, available without medical prescription. The active ingredients will be studied individually although they are generally associated together in weight loss supplements. When taken alone, these dietary supplements can lead to moderate weight loss (1 to 3 kg in most cases). It is thus recommended that dietary supplements be systematically associated with healthy dietary habits and regular physical activity in order to obtain optimal weight loss results.

PART 4: ACTIVE INGREDIENTS IN WEIGHT LOSS DIETARY SUPPLEMENTS

Dietary supplements intended for weight loss can be found everywhere. Their popularity can both be attributed to the pressure of fashion and media as well as to the real consequences of being overweight. They can be found in pharmacies, supermarkets, specialized stores or on the internet with a large diversity in the range of products available. They claim to help obtain a flat abdomen, to eliminate cellulite, to obtain a harmonious silhouette, or simply to help lose weight.

Weight-loss supplements typically fall into the following categories depending on their hypothesized mechanism of action: fat absorbers that block the absorption of fat, gluco-capturers, detoxifiers and drainers, destocking agents, stimulants that increase thermogenesis, and products that suppress appetite or give a sense of fullness. At least one example in each category will be reviewed, in terms of their presentation, sources, active components, supposed mechanism, dosages found in supplements toxicity and side effects.

In this section we will start with a brief introduction on weight loss dietary supplements in general, followed by summary charts on selected active ingredients, at least one example has been chosen per category. Lastly green tea and glucomannan will be studied more in depth due to the widespread use of green tea in dietary supplements and due to the EFSA claims on weight loss and the scientific recognition of the weight loss potential of glucomannan.

1. Weight loss dietary supplements in general

There are over 200 “weight loss” active ingredients. They are generally plant extracts, and their doses are often absent from the dietary supplements’ packaging. The most frequently found ingredient in these products is green tea. Each product can contain between one and thirty active ingredients. Over half of the products sold contain 1 to 5 active ingredients. In general the main ingredients found include: green tea, guarana, chrome, meadowsweet, *Citrus auratium,* pineapple, raisin, mate, dandelion, and more recently chitin, and glucomannan. Other more rare active ingredients include maritime pine, calcium, cranberry, rooibois, greater celandine, horse chestnut, pea, ivy, etc.

These active ingredients can be included into numerous pharmaceutical forms such as capsules (which are the majority), liquids to drink, vials, tablets, powder in packets, cubes to chew, etc. In addition, dosage frequency varies from 1 to 6 units (capsules, vials, etc.) per day, twice a day in general.

In terms of safety, the problem of possible interactions between the numerous ingredients in certain dietary supplements should be brought up, as well as the lack of contra-indications clearly written on the packaging. On a more positive note, the RDA (Recommended Daily Allowance) is often well established on products.

The price of dietary supplements varies enormously, going from 6 Euros to 30 Euros per box or bottle. The majority is situated between 15 and 20 Euros. It is difficult to calculate the price of a complete slimming treatment since the duration isn't always mentioned clearly on the packaging and sometimes more than one box or bottle is needed for one treatment.

In terms of product efficiency, it is difficult to obtain information on products because laboratories rarely publish their clinical studies. In addition the duration or dosage tested can be different than what is recommended in the product. The studies are rarely done against placebos. Lastly, the trials often include few patients, rendering the statistical significance difficult to interpret.

2. Classes and examples of weight loss ingredients

There are several classes of weight loss ingredients in dietary supplements. The five main classes are:

-The "fat absorber/ capturer" (chitosan)

-The "gluco-capturer " (chromium)

- The "detoxifiers and drainers" (orthosiphon, meadowsweet)

-The "fat burners" who increase the basal metabolic rate, also known as destocking agents (L-carnitine, conjugated linolic acid) or thermogenics (caffeine, green tea)

-The satiety increasing supplements (glucomannan, pectin)

In each of these classes one or more active ingredients classically found in each category will be briefly presented. Specific attention will be brought to **green tea and glucomannan from konjac** since these two ingredients have shown significant effects on weight loss. Firstly green tea, which is part of the "fat burners" category, will be studied with particular attention since it has shown to help support weight loss diets by increasing elimination, thought it doesn't have a direct effect on adipose tissue. Secondly, konjac glucomannan, by increasing the sensation of satiety, has shown short term indirect effects on weight loss in

the context of a hypo-caloric diet. Caffeine and L-carnitine's thinning effect have yet to be proven thanks to stronger scientific evidence. Until then, their efficiency should be regarded with precaution (Bertrand, 2011; Cottin, 2011).

In the next pages, summary charts of certain active ingredients will be developed. Each category is illustrated by an example in a chart except for the thermogenic green tea and the satiety increasing glucomannan which will be explored in more detail. The charts contain the active ingredient's name, the category it belongs to, the main components responsible for the activity, the source(s) where the ingredient can be found, the supposed mechanism(s), the dosages found, the eventual side effects and toxicity, the contra-indications, examples of finished products, and a quick conclusion.

2.1 Fat absorber: Chitosan

Active ingredient	**Chitin/Chitosan**
Category	« Fat absorber »
Principal Component responsible for the activity	Chitin (also known as chito-oligo-oligosaccharide) is an amino-polysaccharide containing β-(1,4)-linkages. Chitosan, is the principal chitin derivative and is a hetero-polysaccharide consisting of linear β-1,4-linked GlcNH2 and GlcNAc units. Chitosan is obtained from Chitin by enzymatic (deacetylation), or chemical (NaOH) means. The Difference between chitosan and chitin is the deacetylation degree (inferior to 50% = Chitosan, superior to 50% = Chitin). The higher the deacetylation degree, the more amine groups are present, the more cholesterol and fatty acids can be attached (Rodriguez MS *et* Alberto, 2005). Chitosan is a carbohydrate polymer and an insoluble fiber (98% of insoluble fraction). It is biocompatible and biodegradable (Steffolo *et al.,* 2011).
Source(s)	Chitin can be obtained from the exoskeletons of arthropods (for example: shrimp *(Pleoticus mülleri)* waste) and cell walls of most fungi (Steffolo *et al.,* 2011).
Supposed mechanism	**Reduction of fat absorption in the intestine.** Chitosan behaves as a dietary fiber. It is not absorbed in the intestine because it is resistant to hydrolysis by human endogenous enzymes. Its amino groups, thanks to the free double bonds on the nitrogens, can attract and fix biliary acids, fatty acids and dietary lipids. The bonds created are hypothesized to not be metabolized, thus the fats should not be absorbed by the body and will be eliminated. Chitosan can fix about 4 to 5 times its weight in lipids (*in vitro*) (Rodriguez MS *et* Alberto, 2005)
Side effects/ toxicity	Preliminary studies show that long term consumption of chitosan at high dosages can **reduce the absorption of Calcium magnesium, selenium, iron and vitamins A, D, E and K** (Deuchi *et al., 1995;* Steffolo *et al.,* 2011; Wada *et al.,* 1997).
Contra-indication/interactions	Contraindicated for people allergic to crustacean foods, for children, and for pregnant or lactating women. Interactions: can disrupt the absorption of certain minerals such as zinc and iron and substances such as flavonoids. Can also disrupt the absorption of numerous drugs (Berthrand, 2011).

Ex of finishedproducts	   
Conclusion	To be effective, chitosan must have a deacetylation degree of 89% minimum (to be able to fix fatty acids and cholesterol in the intestine) and must have a size of 40kDa or less. Unfortunately this information is rarely mentioned on packaging. Although Chitosan has a renowned fat absorbing mechanism, it has not shown sufficient its clinical effects in weight loss.

2.2 Gluco-capturer: Chromium

Active ingredient	**Chromium**
Category	"Gluco capturer"
Principal Component responsible for the activity	Trivalent chromium notably **chromium picolinate** has been reported to be the most bioavailable form compared to the other trivalent sources such as chromium chloride, chromium sulphate, chromium lactate, and chromium nitrate (Bertrand, 2011).
Source(s)	Chromium is an essential trace element in human physiology. Brewer's yeast and giblets are the foods with the highest levels of chromium. Other dietary sources include broccolis, green beans, potatoes, whole grain cereals, gruyere cheese, prunes, mushrooms, asparagus, meats, egg yolk, and beer (Cotte *et* Duret, 2010; Bertrand, 2011).
Supposed mechanism	Chromium is an essential metal, but only traces of trivalent chromium are used in the human body for glucose conversion by insulin-driven reactions in carbohydrate metabolic pathways (Golubnitschaja *et* Yeghiazaryan, 2012). It is difficult to establish plasmatic concentrations of chromium due to the absence of reliable biomarkers. Only supplementation can show a deficit in chromium. It has been established that chromium deficit can lead to an elevated plasmatic insulin levels, an increase in plasmatic glucose, cholesterol, LDL cholesterol, and triglycerides levels, as well as a decrease in plasmatic levels of HDL cholesterol and an alteration of immune functions. The above signs of lack of chromium seem to be accompanied by an increased risk of cardiovascular diseases and diabetes (Cotte *et* Duret, 2010; Mooradian, 1994; Bertrand, 2011).

	Chromium's mechanism of action is not completely established today. The **first hypothesis** is that chromium **increases the number of insulin receptors, modifies the insulin-receptor bond and increases insulin sensitivity** (Althuis *et al*. 2002). The **second hypothesis** is that chromium bonds to chromodulin (protein that participates to the regulation of insulin) in response to insulin secretion, which stimulates the activity of the insulin receptor's tyrosine kinase, leading to an **amplification of the insulin signal**. Chromium thus could facilitate the entrance of glucose in the cells and enable its rapid use (Horvath *et al,* 2008, Vincent, 2004).
Dosage	In 2001, in France, the recommended dietary intake was established at 50 µg/day. The average chromium consumption through typical French dietary habits is of about 77 µg/day covering the population's needs through diet. Thus, naturally available food sources used in well-balanced diets are capable of covering the requirement of trivalent chromium completely (Golubnitschaja *et* Yeghiazaryan, 2012). In France the maximum dosage accepted in dietary supplements is of 25 µg/day (Arrêté, J.O.n°123 du 28 mai 2006). Dietary supplements are generally dosed at 25 µg/day in France. In the USA, chromium picolinate is commonly supplied in the range of 200–500 µg/day. It is thus important to beware of the dosages used in clinical tests on chromium picolinate. Indeed if a dosage of 500 µg/day is used in a clinical trial, it is unlikely that the same effects could be obtained at 25 µg/day.
Side effects/ toxicity	Toxicity data in literature concern essentially chromium picolinate (Golubnitschaja *et* Yeghiazaryan, 2012). A controversial issue is whether chromium causes cancer when ingested (Smith *et* Steinmaus, 2009). Certain in vitro and preclinical studies have shown the clastogenic activity of chromium picolinate. Certain authors even consider it to be mutagenic (Golubnitschaja *et* Yeghiazaryan, 2012). The EFSA (European Food Safety Authority) Panel concluded in 2009 that "the use of chromium (III) picolinate, as a source of chromium, is of no safety concern provided that the amount of supplemental chromium does not exceed the level of **250 µg/day**, the value set by the World Health Organization" they also add that the safety of chromium (III) might need to be reevaluated in light of recent reviews and evaluations pointing at conflicting outcomes of genotoxicity assays and reporting diverging views and conclusions on the consequences of this genotoxicity issue (Arrêté, J.O.n°123 du 28 mai 2006; Bertrand, 2011). Case reports have described acute kidney failure, liver damage and anaemia by taking high dosage of chromium picolinate as a dietary supplement as well as adverse cutaneous reactions. Chromium picolinate may possibly affect the levels of neurotransmitters leading to potential risks for patients treated for depression, bipolar disorder and schizophrenia. Globally, chromium picolinate supplements seem to be hormone-related and may influence hormone secretion through their function in the endocrine and metabolic system (Golubnitschaja *et* Yeghiazaryan, 2012).
Contra-indication/ interactions	There is a possible risk of blood glucose levels dipping too low if chromium picolinate is combined with diabetes treatments (Golubnitschaja *et* Yeghiazaryan, 2012).. Corticosteroids, calcium carbonate and antacids can lower the level of chromium in the body (Bertrand, 2011). Intake of chromium supplements and zinc supplements, calcium carbonate or antacids should be spaced out of at least two hours (Cotte *et* Duret, 2010; Bertrand, 2011).

Ex of finished products	
Conclusion	It is reported that chromium picolinate generates sales of more than US$100 million annually. However, over a decade of human studies with chromium picolinate indicate that the supplement has not demonstrated effects on the body composition of healthy individuals, even when taken in combination with an exercise training program. Indeed, when analyzing the results of chromium picolinate supplementation studies, two types of populations appear: the general healthy population for whom no response is observed when supplemented and specific populations (elderly people, patients with metabolic syndrome and patients who have type two diabetes) for whom there is a chromium deficit and who can respond to chromium supplementation according to the form, dose and duration of supplementation (Golubnitschaja *et* Yeghiazaryan, 2012). Potential weight loss thanks to chromium picolinate therapy has not been clearly confirmed. After an evidence-based search into the issue, the US Food and Drug Administration concluded that the 'relationship between chromium picolinate intake and insulin resistance is highly uncertain'. In addition, recent studies have concluded that 'chromium picolinate does not seem to improve key components of metabolic syndrome in obese non-diabetic adults (Golubnitschaja *et* Yeghiazaryan, 2012; Mertz, 1998; Scientific Committee on Food, 2003; Stearns *et al.*, 2002).

A trace element *is a mineral element present in the human body at concentrations inferior to one milligram per kilogram of body weight.)

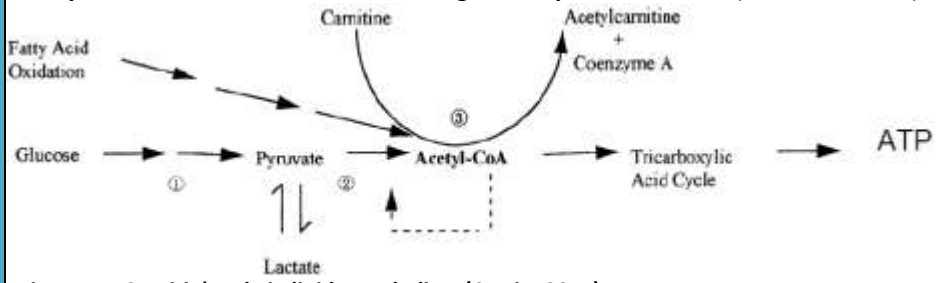
2.3 Detoxifier and drainer: Meadowsweet

Active ingredient	Meadowsweet (Reine-des-prés)
Category	"detoxifiers and drainers"
Principal Components responsible for the activity	Phenolic heterosides (0,3 to 0,5%) such as monotropitoside and spiraneine (salicylic derivatives). Flavonoids such as spiraeoside, rutoside, hyperoside. Hydro-soluble tannins: ellagitanins which represent 10 to 20 percent of the drug (Pharmacopée Fraçaise, 1986).
Source(s)	*Filpendula ulmaria* L. The flower blossoms are collected before their complete bloom and dried in the dark (Bertrand, 2011).
Supposed mechanism	Meadowsweet is claimed to have diuretic and digestive effects in numerous slimming dietary supplements. The extracts' flavonoids and potassium salts are responsible for the diuretic effects. The conjugated effect of the flavonoids and the phenolic heterosides are supposed to facilitate bile evacuation (Bertrand, 2011; Vidal, 2010) but very little scientific data on its clinical efficacy on weight loss is available today.
Dosage	The different dosages for each form are: -**Infusion:** Let infuse (20 mg/L) for 10 minutes. Drink 500ml per day split 3 times a day. -**Tincture:** 20 to 25 drops before meals at breakfast, lunch and dinner -**Glycerin extract of the fresh plant:** 1 tea spoon before meals at breakfast, lunch and dinner -**Integral suspension of the fresh plant:** 1 measure of 2,5 ml, diluted in a half glass of water, before meals at breakfast, lunch and dinner. -**Powder form:** 1 capsule before meals at breakfast, lunch and dinner. -**Dry extract (nebulisate):** 1 to 3 grams per day in capsules to be taken split into 2 or 3 times (Bertrand, 2011).
Side effects/ toxicity	No side effects known as of today besides possible dry skin if you do not drink enough water and become dehydrated while taking supplements of this plant.
Contra-indication	The plant contains salicylic derivatives and thus should be taken with precaution by people allergic to salicylic derivatives or patients taking anti-coagulants (AFSSA, 2007; Bertrand, 2011). There are no restrictions for pregnant or lactating women (Bertrand, 2011).

Ex of finished products	
Conclusion	The weight loss effect of meadowsweet has not been demonstrated for humans; the plant's use is entirely empirical. It only leads to water loss, not fat loss. It does not have an action on adipose tissue but promotes the elimination functions which could be interesting when used in addition to a weight loss diet. Dietary supplements containing this plant may cause weight loss due to dehydration which is not recommended. Its efficacy is questionable and cannot replace the weight loss efficiency of a hypocaloric diet.

2.4 Destocking agents

2.4.1 L-Carnitine

Active ingredient	**L-Carnitine**
Category	"fat burner": destocking agent
Principal Component responsible for the activity	Carnitine, also known as vitamin B11 is a water soluble quaternary amino acid. It has two stereoisomers: L-carnitine and D-carnitine. L-carnitine is the natural and biologically active form. D-carnitine is biologically inactive and can negatively influence the use of the first isomer.
Source(s)	L-carnitine is naturally present in the organism, it is endogenously produced from lysine and methionine but can also be brought by dietary sources (meat, fish, dietary foods).
Supposed mechanism	**Increase in energetic metabolism:** L-Carnitine plays an important role in the in the lipid metabolism; it is necessary for the production of energy from fatty acids. More than 95% of the body's carnitine pool is in skeletal muscle, where it fulfils two major metabolic roles. Firstly, in mitochondrial fatty acid translocation carnitine is a substrate for the enzyme carnitine palmitoyl-transferase 1 (CPT1). In other words, L-carinitine **enables the transportation of long chain fatty acids into mitochondria** which is a prerequisite for β-oxidation. β-oxidation is the production of energy in the myocytes by the transformation of fatty acids into energy in the form of adenosine triphosphate (ATP). However, it has never been proven that the limiting factor for the use of fatty acids by mitochondria is the carnitine dependant transportation system (Brass, 2000). - Secondly, **it participates to the regulation of the ratio coenzyme A (CoA) and acetylCoA in the mitochondria which regulates lipid metabolism** (Wall *et al*, 2011).  **Figure 11: Carnitin's role in lipid metabolism (Cottin, 2011).**
Dosage	Food in an average omnivore diet brings about 20 to 200 mg per day. This quantity is considered to be sufficient even in the absence of endogen synthesis (Cynoder *et* Fricker, 2010). It is difficult to report a supplementation dosage limit since L-carnitine has an endogen source. The DGCCRF (The French General Directorate for Fair Trading, Consumer Affairs and Fraud Control) suggest a **maximum dose for supplementation of 2000 mg/day which is considered to be safe** (risk free) by the ANSES (French Agency for Food Environmental and Occupational Health & Safety).
Side effects/ toxicity	At doses superior to 4 g/day possible side effects include gastrointestinal disorders such as diarrhea. Certain individuals supplemented at a dose of 100 mg/Kg/day reported fish smelling body odor (Cottin, 2011; Cynoder *et* Fricker, 2010).
Contra-indication	Pregnant or lactating women as well as people with epilepsy should not take L-carnitine supplementations (Cottin, 2011).

Ex of finished products	
Conclusion	Many studies show that L-carnitine can improve the use of energy. But this effect needs to be proven in terms of weight loss. As of today, clinical studies carried out have not shown significant weight loss following L-carnitine supplementation. Its mechanism that accelerates lipid oxidation has been proven but it has yet to prove its effectiveness in weight loss (Cottin, 2011; Cynoder *et* Fricker, 2010).

2.4.2 CLA : Conjugated Linoleic acid

Active ingredient	**CLA : Conjugated Linoleic acid**
Category	"fat burner": destocking agent
Principal Component responsible for the activity	CLA isomers are essential fatty acids from the omega 6 family. There are over 28 different CLAs. An anti-obesity effect has been attributed to Trans -10, Cis-12 CLA.
Source(s)	Cis-9, Trans-11 CLA and Trans-10, Cis-12 CLA are naturally found in foods at a respective proportion of about 70% and 30% (different proportions possible in supplements). It can be found in milk, butter cheese, eggs, meat especially beef and lamb, and safflower oil (AFSAA, 2005).
Supposed mechanism	**A possible mechanism is an increase in the energetic metabolism an increase in fat burning.** Recently, the Trans-10, Cis-12 CLA but not the cis-9,trans-11 CLA isomer was shown to significantly increase lipolysis in human adipocytes . CLA was also shown to modify hormone sensitive lipase expression, key component of fatty acid utilization. Moreover, CLA is hypothesized to reduce fatty acid synthesis in adipocytes, suggesting that CLA could discourage fat deposition directly contributing to body composition (Vaughan *et al.*, 2012). These mechanistic hypotheses should be further studied since there is very restrained clinical efficacy support (AFSAA, 2005 ; AFFSA-saisine n° 2006-SA-0156).
Dosage	2,6 grams per day of Trans -10, Cis-12 CLA isomer; or 1,7 to 6,8 grams per day of a mix of Cis-9, Trans-11 CLA and Trans-10, Cis-12 CLA isomers (AFFSA-saisine n° 2006-SA-0156; Bertrand, 2011).
Side effects/ toxicity	-Possible reduction of insulin sensitivity for Trans-10, Cis-12 CLA -Possible reduction of HDL cholesterol and increase of LDL-cholesterol -Possible reduction of Apo B -Possible increase in urinary isoprostanes (8-isopgf2α). This increase in oxidative stress is considered due to the Trans-10, Cis-12 CLA isomer. -Possible increase in the plasmatic C-Reactive Protein (CRP) for Trans-10, Cis-12 CLA

	-Possible reduction of lipids in milk -Possible induction of diabetes due to the reduction of insulin sensitivity -Possible slight gastrointestinal disorders and tiredness (AFFSA-saisine n° 2006-SA-0156).
Contra-indication	Due to the absence of toxicological data, it is recommended that pregnant woman, children, and people with liver disorders do not exceed the normal dietary dose of CLA that is of approximately 1 gram per day (AFFSA-saisine n° 2006-SA-0156).
Ex of finished products	
Conclusion	Side effects must be taken into consideration, especially since the beneficial effects are of small amplitude. AFSSA considers that the use of CLA isomer mixes in dietary supplements for humans is not justified.

2.5 Increase of basal metabolic rate and thermogenics: caffeine and green tea

Active ingredient	**Caffeine**
Category	fat burner": thermogenic
Principal Components responsible for the activity	**Caffeine** is a bitter, white crystalline xanthine alkaloid. It is also called 3,7-dihydro-1,3,7-trimethyl-1H-purine-2,6-dione.
Source(s)	Coffee beans (*Coffea Arabica, Coffea anephoria, variety robusta:* 0,6 to 3 % of caffeine*)* cacao beans (*Theobroma cacao: 0,1* to 0,4 % of caffeine*)*, tea bush leaves (*Camellia sinensis L:* 2 to 4 % of caffeine in leaves.), kola nut (*Cola nitida, Cola acuminate* 1 to 3,5 % of caffeine), yerba mate (*Ilex paraguaryensis:* approx. 1 % of caffeine), guarana berries (*Paullina cupana:* 3,5 to 5 % of caffeine) (Heckman *et al.,* 2010; Vidal, 2010).
Supposed mechanism	**-Thermogenic:** Caffeine has been shown to stimulate thermogenesis and the oxidation of fatty acids in part through inhibition of the phosphodiesterase enzyme and antagonism of the adenosine receptors thus stimulating the sympathetic nervous system stimulation of thermogenesis (Cottin, 2011).
Dosage	Should be inferior to 300 mg/day total for all sources combined.
Side effects/ toxicity	**General opinion: no secondary effects for consumption inferior to 300 mg/day.** In Europe, the average consumption is of 200 mg/day. Experts consider that the consumption of caffeine at doses superior to 500 mg to 600 mg is unreasonable and abusive. **Excessive consumption of caffeine leads to numerous side effects.** **-(≥600 mg/day):** Excitability, irritability, nervousness (starting at ≥ 210 mg/day for certain patients), insomnia, heart rate alteration, agitation, head ache at high doses

	-(≥1000 mg/day): The effects above plus possibly vomiting, convulsions, light delirium at very high doses **-Short term lethal dose:** 5 to 10 g/day, which is equivalent to 75 cups of coffee, 125 cups of tea or 200 cola based drinks (Afssa, 2007; Cottin, 2011; Curatolo et Robertson, 1983). **-Regular consumption can lead to addiction, and withdrawal symptoms** such as headaches, tiredness, confusion, irritability, nausea, anxiety, delirium, and muscular tension (Heckman *et al.,* 2010).
Contra-indication/ interactions	People suffering from insomnia, cardiac disorders, anxiety disorders, high blood pressure, stomach or renal problems should limit their caffeine consumption. Pregnant women should limit their consumption of caffeine to less than 300 mg/day to avoid fetal abnormalities (Afssa, 2007; Cottin, 2011; Heckman *et al.*, 2010). In addition, it is important to take into account daily caffeine consumption before taking dietary supplements containing caffeine or plants containing caffeine to avoid side effects. **<u>Interactions:</u>** -Avoid taking fluoroquinolones (antibiotics) with caffeine (because they increase caffeine's kinetic (increase of half life) which can increase the risk on overdose. -Avoid taking with phenytoin (antiepileptic) because caffeine decreases the half life of phenytoin which can lead to a reduced efficacy of the treatment. -Caffeine can inhibit or increase the effects of certain drugs because it is metabolized by the enzyme CYP1A2 which is a key enzyme for the metabolism of numerous drugs with a psychotropic activity (antidepressants, antipsychotics). -Lastly, Caffeine should never be taken with plants containing stimulating substances close to amphetamines (ephedra, bitter orange, etc.) due to the risk of a stroke (Cottin, 2011, Heckman, 2010).
Ex of finishedproducts	
Conclusion	The effects of caffeine on thermogenesis and fat oxidation exist but are limited. The effects are more important in thin subjects compared to obese subjects. Its effect is increased by physical activity. Studies do not show significant results on long-term weight loss, which is most likely linked to a certain acquired tolerance to caffeine (Kovacs *et al,* 2004; Westerterp-Plantenga, 2005 ; Westerterp-Plantenga, 2010). Today the use of caffeine in dietary supplements is not justified and can lead to the risk of overdose when taken with other caffeine sources.

3. Focus on green tea

Green tea and caffeine are thermogenics, which means they increase the production of heat by the body, thus increasing the beta-oxidation of fatty acids from the adipose tissue. Thermogenics increase the basal metabolic rate which promotes a negative energy balance. In this thesis the star ingredient green tea, which notably contains caffeine, will be studied.

3.1 General presentation of green tea and history of use

Tea comes from tea bush leaves (*Camellia sinensis*, Theaceae). It is a popular beverage which benefits from a worldwide consumption second only to water (Hursul *et al.,* 2009). There is a long history of consumption of tea in the human diet (approximately 5,000 years). According to traditional Chinese belief, tea seems to be effective in the control of body weight.

The 3 main types of tea: green, black, and Oolong, represent respectively 20, 78, and 2% of world tea consumption, differ in terms of processing and chemical composition.

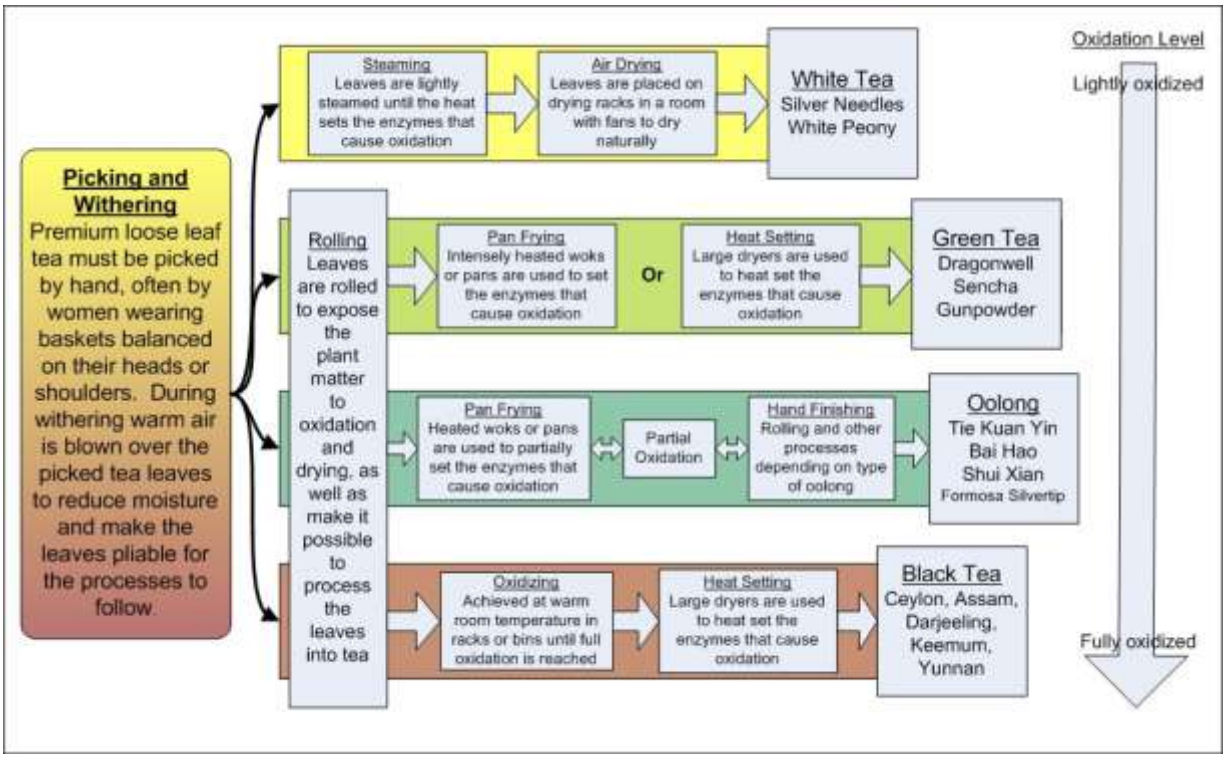


Figure 12: Tea processing chart (Davis et al., 2013).

As mentioned above, each type of tea (Oolong, black, green, etc. comes from the same plant. The differences come from the treatment of the leaves (drying, roasting, fermentation, etc.). Polyphenols are oxidized during fermentation. Green and white teas are richest in polyphenols since they are not fermented. (Bertrand, 2011; Grove *et* Lambert, 2010).

In the processing of green tea, leaves are steamed or pan-fried to inhibit polyphenol oxidase activity. In contrast, black tea is produced by crushing the tea leaves and allowing them to undergo an enzyme-mediated oxidation process known as fermentation. According to the monograph of green tea in the French Pharmacopeia, the leaves must be yellow, non-fermented, rapidly desiccated by heat, and then dried. The dried leaves must contain at minimum 2% of caffeine, calculated according to the mass of dried drug (Bertrand, 2011; Grove *et* Lambert, 2010).

Chemically, green tea is characterized by the presence of large amounts of polyphenols known as catechins. The main active molecules in green tea are polyphenols, caffeine, theophylline, and theobromine (Bertrand, 2011; Grove *et* Lambert, 2010).

3.1.1 General presentation of tea polyphenols

Green tea contains high quantities of several polyphenolic components, most of which are flavonoids (also known as flavan-3-ol or catechins) such as epicatechin, epicatechin gallate, epigallocatechin, and, the most abundant and probably the most pharmacologically active, epigallocatechin gallate (EGCG) (Diepvens *et al*., 2007).

Polyphenols are compounds found in many natural sources. They are the pigments responsible for the color of many flowers and fruits. They protect plants from the deleterious effects of UV radiation. A cup of tea contains about 80 to 100 mg of polyphenols (Bertrand, 2011; Grove *et* Lamber, 2010; Vidal 2010).

Green tea also contains polymerized catechins which are also known as tannins. Procyanidines are well represented in green tea, they are polymers of epicatechin gallate, prodesphinidines and epigallocatechins (Bertrand, 2011).

3.1.2 General presentation of caffeine

A cup of tea contains about 50 mg of caffeine (Vidal, 2010). Caffeine is the world's most frequently ingested psychoactive substance and one of the most commonly consumed dietary ingredients throughout the world. About 80% of caffeine consumed is in the form of coffee, tea being the second predominant source (Heckman *et al.*, 2010).

Caffeine is an alkaloid, which is a substance produced as an end product of nitrogen metabolism in certain plants. Caffeine can be prepared by extraction from natural sources or by synthesis from uric acid. Indeed, caffeine is present in many plants, notably in coffee beans, cacao beans, the leaves of the tea bush, as well as the kola nut, yerba mate, and the guarana berries (Heckman *et al.*, 2010; Vidal, 2010).

Caffeine belongs to the family of heterocyclic compounds known as purines. Caffeine's systematic name is 3,7-dihydro-1,3,7-trimethyl-1H-purine-2,6-dione; but is also called 1,3,7-trimethylxanthine, and 1,3,7-trimethyl-2,6-dioxopurine. Pure, it appears as white crystals that are bitter. Caffeine's chemical formula is $C_8H_{10}N_4O_2$ and is soluble in water and in numerous organic solvents. (Pharmacopée Française Xème edition, 1986; International Occupational Safety and Health Information Centre (CIS), 2012).

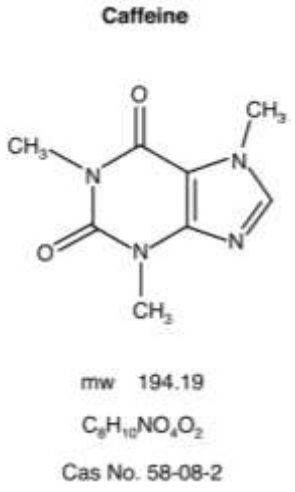


Figure 13: Caffeine's chemical structure (Dunnick et al., 2007)

Tea leaves contain caffeine (2 to 5 % by weight) and catechins. The caffeine content in tea depends on the parts of the plant used:

-first and second leaves: 3.4%
-fifth and sixth leaves: 1.5%
-flower: 0.8 %
- green fruit skin: 0.6 %
-seed: 0% (Westerterp-Plantenga MS, 2010).

3.2 Supposed mechanism of action

3.2.1 Mechanism linked to polyphenol content

Tea polyphenols have been shown to inhibit *de novo* lipogenesis, increase lipid oxidation, increase carbohydrate utilization, and decrease carbohydrate uptake (Grove *et* Lamber, 2010).

The supposed mechanism of catechins or green tea polyphenols is the inhibition of cathecol-O-methyl-transferase (COMT) and a synergetic stimulation of thermogenesis along with caffeine. Noradrenalin is inactivated by enzymes such as the monoamine oxidase (MAO) or the COMT, which leads to the reduction of thermogenesis (Westerterp-Plantenga, 2010).

The inhibition of COMT and MAO promotes noradrenalin's (NA) role in thermogenesis stimulation. This inhibition has been studied *in vivo* by analyzing the urinal excretions of NA, which is increased by the action of inhibiting enzymes.

3.2.3Mechanism linked to caffeine content

Caffeine is thermogenic, which means it increases the production of heat by the body, thus increasing the beta-oxidation of fatty acids from the adipose tissue. It thus increases the basal metabolic rate which promotes a negative energy balance (Bertrand, 2011).

The precise mechanism by which caffeine influences thermogenesis has not yet been evaluated. As of today, its action, at sufficiently high doses (about 150 mg of caffeine, corresponding to approximately 3 cups of tea) seems to be the sum of different synergetic mechanisms which are essentially:

-The increase in plasmatic catecholamine
-The inhibition of phosphodiesterase enzymes (thus leading to the accumulation of AMPc which increases the effect of catecholamins and thus increases thermogenesis)
-An antagonist effect on adenosine receptors (which increases catecholamins).

At doses achieved in normal human consumption, caffeine's main effect is on the central nervous system as a stimulant that interacts with the adenosine receptor and can also interact with adrenergic, cholinergic, GABA, or serotonin receptors, the implications of which are unknown. (Brent, 2011; Shi *et al*., 1993; Leon, 2005a,b).

To conclude, **caffeine can modify the organism's energetic metabolism and increase thermogenesis.** The metabolic heat generated during thermogenesis notably comes from lipolysis, thus **caffeine has an indirect lipolytic action.**

3.2.3Mechanism linked to theophylline content

Green tea also contains theophylline. Theophylline has a diuretic effect, which is clearly marked in tea.

3.3 Efficacy of green tea and its components on weight loss and stabilization

3.3.1 Epidemiological studies

A limited number of epidemiology studies have looked into the impact of tea on body weight and other markers related to obesity. A 2003 cross-sectional epidemiological study of 1103 Taiwanese adults found that habitual tea drinkers (defined as a person who consumes tea at least once per week for 6 months) who consumed tea for over 10 years had lower percentage body fat (19.6% decrease) and waist/hip ratio (2.1% decrease) compared with non-habitual consumers (Wu *et al.*, 2003). In this study, black tea was less frequently consumed whereas green tea and Oolong tea were consumed more frequently(1.6% vs. 41.3). A longitudinal analysis within The Netherlands Cohort study of 4280 adults found an inverse relationship between catechin consumption and a BMI increase over the 14 year study period (Hughes *et al.*, 2008). The BMI increases for the lowest and highest quintiles of catechin consumption were respectively of 0.77 and 0.31 kg/m².

3.3.2 Human intervention studies and preclinical studies on green tea and weight loss

The health properties of green tea are largely attributed to polyphenols, compounds with potent antioxidant properties (Trevisanato *et al.*, 2000) as well as caffeine. Studies suggest a role of green tea polyphenols and caffeine on energy expenditure. Moreover, the stimulatory effects of a catechin-caffeine mixture (as in green tea) on energy expenditure cannot be completely attributed solely to its caffeine content because the thermogenic

effect of a catechin-caffeine mixture is greater than that of an equivalent amount of caffeine (Hursel *et al*., 2009; Westerterp-Plantenga, 2010).

In-vitro studies have shown an indirect activity of green tea polyphenols on adipocytes metabolism. These findings suggest that catechins have a positive effect on weight control by inhibiting the transformation of preadipocytes in adipocytes differentiation (Furuyashiki T *et al.* 2004).

Dullo *et al.* demonstrated in a controlled study that the administration of 270 mg of EGCG (obtained from a standardized extract of green tea) produced a 4% increase in energy expenditure, a 35% increase in fat oxidation and a 40% increase in the concentration of NA in urines compared to normal. These results are thought to be due to the inhibiting action of EGCG on the enzymes responsible of NA catabolism (Dullo A.G. *et al*., 1999 ; Dullo A.G. *et al*., 2000).

The effect of ECGC on COMT in mice has also been studied. All green tea gallate-catechins have an effect of COMT but EGCG's effect is the most important. Bose *et al.* reported that mice treated with 7.0 mmol/gram dietary EGCG for 15 weeks reduced body weight gain (33–41%) in high-fat fed male mice compared with high-fat fed controls. In addition, the EGCG-treated mice had significantly lower adipose tissue weight. The EGCG-treated mice had higher fecal lipid concentrations compared with the high-fat–fed mice; there was a strong inverse correlation between fecal lipid content and body weight gain. These results suggest that EGCG-mediated modulation of dietary fat could be responsible for the decrease in body weight observed in the EGCG-treated mice (Bose *et al.*, 2008).

A study including 240 obese, Japanese participants treated with a catechin-enriched green tea beverage (583 mg of catechins) or a control green tea beverage (96 mg of catechins) once daily for 12 weeks (Nagao *et al,.* 2007) studied body weight fluctuations. Participants consuming the high catechin beverage had a significant body weight decrease (2.3% decrease), total fat area decrease (4.9% decrease), and visceral fat decrease (9.4% decrease) compared with baseline values. Percent body fat, waist and hip circumference were significantly decreased compared to the baseline. All of these decreases were more important in the high-catechin–treated group than in the low catechin controls.

Similar results were also reported in a study including Japanese subjects with type II diabetes that were given 72.3 or 582.8 mg catechins in 1 can of green tea beverage per day (Nagao *et al.,* 2009). After the 12-wk period, the participants taking 582.8 mg of catechins had a significant decrease in waist circumference (3.67%) and systolic blood pressure (4.34%) compared to baseline values.

The results of studies on green tea intake and its influence on BMI waist/ hip ratio, or percent body fat are not always positive. For example, in a randomized trial conducted on 60

overweight or obese Thai subjects, the ingestion of green tea capsules (250 mg each containing 33.6 mg of EGCG, 3 times/day) for 12 weeks resulted in a significant decrease in body weight (3.9%) compared to the baseline and placebo control, but there was no significant effect on BMI, waist/ hip ratio, or percent body fat (Auvichayapat *et al*, 2008). Similar results were observed in a study of 46 overweight women in the Netherlands (Diepvens *et al*., 2005). Treatment with green tea extract (375 mg catechins) for 87 days in combination with a reduced calorie diet resulted in no significant effect on BMI, waist: hip ratio, or fat mass. The doses of tea catechins used in these les positive studies were somewhat lower than those used in the studies that reported positive results. Thus the observed differences may be due to a dose effect.

3.3.3 Human intervention studies on tea and weight maintenance

It is also important to study the effect of green tea on the maintenance of weight following weight loss. A meta-analysis of 11 studies on green tea and weight loss showed that habitual consumption of green tea had beneficial effects on weight loss (mean weight loss of 21.3 kg) and **helped weight maintenance following weight loss**. The effects of green tea were modulated by chronic, high (300 mg/d) intake of caffeine (Hursel *et al. ,*2009).

To illustrate the above statements the study conducted by Westererp-Plantenga *et al*. will be exposed. This study showed that treatment of overweight or moderately obese subjects from the Netherlands (n = 76) with EGCG/caffeine capsules (0.55 mmol/0.77 mmol total daily dose) for 3 months following weight loss **resulted in further decrease in body weight and increased fat oxidation in subjects** who habitually consumed less than 1.55 mmol caffeine/day. In individuals who chronically consumed more than 1.55 mmol caffeine/day, these weight maintenance effects were lost (Westerterp-Plantenga *et al.,* 2005). These results seem somewhat counterintuitive since the increased caffeine consumption should theoretically facilitate weight loss and energy expenditure. The mechanism by which high chronic caffeine consumption affects weight maintenance by EGCG + caffeine is unclear but could be related to modulation of either EGCG or caffeine metabolism (Hursel *et al. ,*2009).

This same meta-analysis showed that all the studies conducted on Asian subjects were positive, contrarily to the studies conducted on Caucasian subjects whose results were often contradictory.

In sum, although the evidence was limited, habitual caffeine intake and ethnicity were found to be possible moderators of weight loss effects. A difference in genetic predisposition of subjects, probably due to multiple variants of the catechol O-methyltransferase (COMT) polymorphism, might explain the discrepancy in the results between studies. (Hursul *et al*., 2009)

To conclude, numerous clinical studies have shown a significant increase in energy expenditure and fat oxidation after administration of green tea. Green tea's action cannot completely be attributed to caffeine since the thermogenic effect was more important with green tea than with caffeine alone for the same doses of caffeine (Westerterp-Plantenga, 2010). In addition, certain long-term studies have demonstrated the efficiency of green tea on weight loss and weight maintenance after a hypo caloric diet (Westerterp-Plantenga, 2010). However, the doses of ECGC and caffeine in the tea extracts are rarely clearly mentioned, making it difficult to compare study results between one another as well as with the results that can be expected with the intake of commercial dietary supplements. According to the studies above, significant weight loss results were obtained with dietary supplements generally containing about 200 mg of EGCG (equivalent to approximately 3 cups of tea) daily associated with caffeine, as well as 580 mg of total catechins daily for variable durations generally of at least 12 weeks.

3.4 Dosage

A cup of green tea contains approximately 50 mg of caffeine and 80 to 100 mg of polyphenols. Green tea supplements typically contain much higher levels of polyphenols than those found in a cup of tea. The therapeutic index of green tea should be established, not only when the compounds are delivered via the diet but also when (as they often are) converted to a bolus formulation (e.g. pill, capsule, tincture).

In a study, different dosages of catechins did not show statistically different results in terms energy expenditure increase. In the study aiming to compare the effect of green tea extracts containing a fixed dose of caffeine and variable doses of EGCG on 24 hour energy expenditure and fat oxidation, fourteen subjects took part to this randomized, placebo-controlled, double-blind, cross-over study. Each subject was tested numerous times in a metabolic chamber to measure 24 hour energy expenditure, substrate oxidation and blood pressure. During each stay, the subjects ingested a capsule of placebo or capsules containing 200 mg caffeine and a variable dose of EGCG (90, 200, 300 or 400 mg) three times daily, 30 minutes before standardized meals. Twenty-four hour energy expenditure increased significantly by about 238Kcal (750 kJ) with all EGCG-caffeine mixtures compared with placebo. The main finding of the study was that the increase in 24 hour energy expenditure was highest with the EGCG-caffeine mixtures compared to pure caffeine. However, this increase was similar with all doses of EGCG in the mixtures (Bérubé *et al*., 2005).

These results show that the smallest dose of 90 mg of EGCG along with 200 mg of caffeine three times daily was sufficient to increase 24 h energy expenditure. This study shows that a dose of 210 mg of EGCG per day (which is equivalent to 3 cups of tea) along with 600 mg of

caffeine is sufficient to obtain significant results. It would be interesting to find a similar study with a lower dose of caffeine, for example 50 mg three times a day, as is found in a cup of tea.

It is difficult to compare studies due to the differences of dosages between different green tea supplements. Indeed studies and dietary supplements rarely put forward a clear standardized EGCG and caffeine content. The extraction process of the green tea is of high importance. As an example, hydro-alcoholic extraction (with 65-75 percent of ethanol) extracts 1,5 to 4,7 times more EGCG than aqueous extraction; which corresponds to approximately 35 mg of EGCG/g of dry green tea. In addition, the age of the tea leaves has its importance. There is more ECGC in tea leaves coming from older tea plants as well as from leaves that are older on a same plant. The origin of the tea plant also causes important fluctuations in the ECGC composition of the tea. In sum, EGCG composition can vary from 1 to 6 times between a young green tea extracted with boiling water and an older green tea extracted with ethanol (Kotzki, 2010).

Without a clear standardization in the composition of the tea extract it is thus almost impossible to know the exact content of EGCG and caffeine. Below are a couple of examples of the information available for green tea supplement consumers:

- “300 mg of aqueuse extract (*Camelia sinensis*) on a maltodextrine support per capsule, take 4 to 6 capsules per day”.
- “250 mg per capsule of 100% pure plant powder of organic green tea. Take 2 to 3 capsules per day.”
- For two capsules: 700 mg of Green tea aqueous extract (*Camelia sinensis* titrated at 80% of polyphones by optic density at 280 nm)”

When buying green tea supplements, it is common to find manufacturers claiming that their products contain "EGCG found in many cups of tea" or "x milligrams of green tea extract". These claims and labels are vague and potentially misleading. Catechins and EGCG being highly active antioxidants, standard extraction processes often end up destroying a high proportion of both. I recommend purchasing products from laboratories and manufacturers who clearly indicate the catechin, EGCG, and caffeine content of their products.

3.5 Side effects and toxicity

The consumption of tea in the human diet has a long history of use (approximately 5,000 years). Throughout this time, there have been few reports of adverse effects with the consumption of tea at usual doses found in human nutrition (Kotzki, 2010).

In general, tea consumption can have **gastro intestinal reflux disease** as a side effect. It is recommended that people suffering from gastro intestinal reflex disease, esophagitis, and hiatus hernia, avoid foods rich in methylxanthin components, such as tea, chocolate, kola, and coffee. These foods can lead to the relaxation of the inferior esophageal sphincter (situated at the entrance of the stomach), which could cause reflux of the gastric content into the esophagus (Bertrand, 2011).

3.5.1 Side effects specifically linked to polyphenols

There is emerging evidence that high doses of tea polyphenols may have adverse side effects, notably the **potential hepato-toxicity of high doses of green tea polyphenols** (Kotzki, 2010). Green tea supplements typically contain 0.4–8 mmol of EGCG and generally recommend the dosage of 1–2 capsules up to 3 times/day; resulting in a total recommended dose of up to 5.2 mmol/day. As mentioned above, although there have been few reported adverse effects associated with green tea beverage consumption, green tea-based dietary supplements are a different dosage form and have the potential to deliver much higher doses of catechins than green tea beverages. From 1999 to 2009, there have been 34 case studies linking consumption of green tea-based supplements to hepato-toxicity (Grove and Lambert, 2010).

3.5.2 Side effects specifically linked to caffeine

An excessive consumption of caffeine leads to numerous side effects. At doses superior to 600 mg/day, caffeine frequently causes anxiety, nervousness (starting at ≥ 210 mg/day for

certain patients), trembling, excitability, irritability, insomnia, heart rate alteration, insomnia, agitation, and head ache at high doses (≥ 600 mg/day). At doses of 1000 mg or more, the symptoms above can progress towards vomiting, convulsions, and light delirium (Afssa, 2007; Cottin, 2011) People suffering from insomnia, cardiac disorders, anxiety disorders, high blood pressure, stomach or renal problems should limit their caffeine consumption. Pregnant women should limit their consumption of caffeine to less than 300 mg/day to avoid fetal abnormalities.

The general opinion is that there are no secondary effects for consumption inferior to 300 mg/day. In Europe the average consumption is of 200 mg/day. It is important to take into account daily caffeine consumption before taking dietary supplements containing caffeine of plants containing caffeine. It is thus recommended to buy dietary supplements clearly indicating caffeine content since it can be variable form one supplement to another. The lethal dose (short term) for an adult is of 5 to 10 g/day of caffeine which is equivalent to 75 cups of coffee, 125 cups of tea or 200 cola based drinks. (Afssa, 2007; Cottin, 2011; Curatolo *et* Robertson, 1983).

It is important to take into account daily caffeine consumption before taking dietary supplements containing caffeine of plants containing caffeine to avoid side effects. Regular consumption of caffeine can lead to addiction, and withdrawal symptoms such as headaches, tiredness, confusion, irritability, nausea, anxiety, delirium, and muscular tension. In addition, the long term effects of caffeine are not completely clear and do not benefit from a consensus of scientific opinions. Research is unclear about the link between caffeine intake and an increased risk of cardiovascular diseases (van Dam, 2008; Reis *et al.,* 2010).

3.5.3 Side effects specifically linked to theophylline

Tea has a diuretic effect due to its theophylline content.

3.6 Interactions

3.6.1 Tea and vegetarians

Polyphenols and tannins can reduce the absorption of **iron contained in plant sources.** Vegetarians who exclusively consume plant iron must be vigilant. This effect can be reduced by avoiding the consumption of tea at the same time as meals, for example one to two hours before or after meals at least (Bertrand, 2011).

3.6.2 Tea and anti-coagulants

Green tea can modify the concentration of anticoagulants drugs in the blood (Coumarine®, Warfilone®, and Sintrom® for example) which necessitates precaution. It is hence preferable for these patients who take these drugs to limit their tea consumption (Bertrand, 2011).

3.6.3 Tea and chemotherapy

A study published in 2009 indicated that green tea supplements were susceptible to reduce the effect of Velcade®, a drug used to treat multiple myeloma (bone marrow cancer) (Golden *et al.,* 2009). The study was carried out on cancerous cells then on a mouse model. The researchers were expecting an increased effect of the anticancer drug thanks to the green tea supplement, but instead found that green tea (notably EGCG protected the cancerous cells from Velcade®'s action. These results were obtained in mice, but by measure of security it is preferable to recommend avoiding taking green tea (infused or in supplement form) while under **chemotherapy.**

3.6.4 Interactions linked to the caffeine in tea

Fluoroquinolones are broad-spectrum antibacterial drugs (for example ciprofloxacin, norfloxacin, and ofloxacin). Caffeine can increase **Fluoroquinolones**'s kinetic (increase of fluoroquinolones' half life) which can increase the risk of overdose. It is recommended to avoid taking fluoroquinolones with caffeine. In addition, Caffeine can decrease the half life of **phenytoin** (an antiepileptic) which can lead to a reduced efficacy of the epileptic treatment. Thus it is recommended to avoid taking with phenytoin with caffeine. In addition, caffeine can potentially inhibit or increase the effects of certain drugs because it is metabolized by the enzyme CYP1A2 which is a key enzyme for the metabolism of **numerous drugs with a psychotropic activity (antidepressants, antipsychotics)** (Bertrand, 2011).

Lastly, Caffeine should never be taken with plants containing stimulating substances close to **amphetamines** (ephedra, bitter orange, etc.) due to the risk of a stroke (Bertrand, 2011).

3.7 Conclusion on green tea

In occidental countries, green tea consumption has boomed in the past years due to its numerous supposed miraculous qualities, notably in weight loss. More rationally and following the above analysis, it can be concluded that certain green tea extracts can have a relative effect on weight regulation. The effects are various, dependant of the dosage of EGCG and caffeine in the dietary supplements, habit dependant (regular caffeine consumption) and even linked to the ethnic origin (Caucasian vs. Asian). The effects are

often significant but not always. In addition, the doses of polyphenols in dietary supplements should not be excessive in order to reduce the risk of hepato-toxicity. Nevertheless, green tea, infused at about 3 cups of tea per day or in supplement form equivalent to about 200 mg of EGCG for one to two months or more seems to be an interesting option to support weight loss so long as it contains dietary doses of ECGC, that subjects under anticoagulants, antidepressants, antipsychotics, phenytoin, or fluoroquinolones as well as subjects who are vegetarian, pregnant or taking anti-cancer drugs limit or completely restrict their consumption of green tea.

4. Focus on glucomannan and other satiety increasing ingredients

The reduction of food intake is one of the most efficient ways to lose weight. Substances reducing hunger sensations can bring helpful support during weight loss periods. Satiety increasing substances are generally hydrophilic (they can absorb large quantities of water), rich in fiber and come from plant, algae, or fruit sources. After ingestion, these substances swell in presence of the water in the gastric content and occupy part of the volume of the stomach. By doing so, these ingredients contribute to reduce the sensation of hunger and slow down the passage of food into the intestines.

Numerous substances are known to increase satiety such as guar gum, carob tree, lemon and apple pectin, Kelp, Nopal, and Konjac .

4.1 Satiety increasing ingredients

4.1.1 Guar gum

This annual grass is cultivated in India, Pakistan, and Texas, as well as in Central America. The crushed albumen is used as a viscous preparation. Its active ingredient is galactomannan.

Guar gum and similar soluble fibers in the regulation of cholesterol metabolism: Current understandings and future research priorities (Rideout, 2008).

4.1.2 Carob tree

This tree from the Mediterranean region has seeds rich in locust bean gum (carob gum). The thickening properties come from polysaccharides derived from mannose (Cottin, 2011).

4.1.3 Lemon and apple

Their pulp is rich in pectins and soluble fibers that are highly adsorbent gelling agents (Rideout, 2008; Vidal, 2010).

4.1.4 Kelp (Fucus)

This seaweed grows on the cold and temperate coasts of the northern hemisphere. Once the dehydrated thallus has been ingested, it rehydrates its self in the stomach, increasing in volume. The increased volume mechanically promotes the sensation of satiety. Kelp also contains a large quantity of fibers which help the intestinal transit. Kelp contains iodine and should not be taken by patients with thyroid problems (Cottin, 2011).

4.1.5 Nopal

Nopal is a cactus from Mexico. It is rich in fibers, notably pectins, mucilages and gums which promote the sensation of satiety when ingested (Ollier, 2011).

4.1.6 Konjac.

This plant originating from Asia has satiety increasing properties thanks to the glucomannan it contains in the tubercle (root).

In this thesis specific attention will be given to this ingredient often found in slimming dietary supplement and claimed to moderate appetite (Cottin, 2011).

4.2 Glucomannan: general presentation and history of use

Glucomannanis a soluble fiber, extracted from the root of a plant from the Aracee family: *Amophorphallus konjac,* cultivated in the east of Asia. Glucomannan has been **safely consumed for over 1000 years** in the Orient (Walsh *et al.,* 1984).

The konjac tubercle (root) is dried and pulverized into flour composed principally of neutral mucilage like glucomannan (Cottin, 2011).

Its viscosity and gelation properties have been used in traditional Japanese cuisine for centuries (Canga *et al.*, 2004). It can be a food additive used as an emulsifier and a thickener, and can also be consumed in the form of food supplements (EFSA Journal, 2010).

4.3 Bioavailability

Glucomannan is a polysaccharide and dietary fiber with a high molecular weight (200-2000 kDa). It is non-digestible in the human small intestine (AFSSA, 2002; EFSA Journal, 2010).

Indigestibility of glucomannan in the small intestine

The indigestibility of konjac fiber in the small intestine was demonstrated experimentally in 1942 when a pancreatic enzyme preparation was unable to release glucose from a konjac flour preparation. To the best of our knowledge, there are no known human digestive enzymes that cleave the ß-1,4 linkages between the glucose and mannose units of the polysaccharide backbone or the ß-1,3 linkages at the branch point (Food Science and Safety Section, National Food Authority, Canberra, Australia). Since glucomannan's polymeric structure is assumed to render it unavailable for intestinal degradation or absorption, it is commonly believed to pass through the gastro intestinal tract unaltered. Studies have shown that glucomannan could be degraded and metabolized by gut bacteria in the colon (McCarty, 2002).

These findings push forward the hypothesis of the indigestibility of glucomannan in the stomach and intestine by human enzymes.

4.4 Supposed mechanism of action

Many studies suggest that fiber intake could play an important role in weight management.

Nutritional guidelines recommend dietary fiber for health promotion and disease prevention (Salas-Salvado *et al.*, 2007). It has been shown that obesity and diabetes are less prevalent in populations consuming large amounts of dietary fiber (Newby *et al.,* 2005).

In addition, as seen previously, it has been shown that repeated episodes of weight loss and regain, known as weight cycling or "yo-yo dieting", are highly prevalent, not only in overweight but also in non overweight individuals (Brownell *et* Rodin, 1994). Following these episodes there are hormonal modifications implicated in satiety sensations and energy

expenditure so that weight regain is physiologically encouraged and facilitated (Sumitrhran, 2011). Indeed, due to calorie restriction at the beginning of the diet, the body secretes a hunger hormone which remains at a higher level even at the end of the diet which will encourage the "yo-yo effect". This mechanism, encouraging weight regain can persist for up to one year after the initial diet. This viscious cycle induces a phenomenon **of weight loss phase resistance with an increased desire to eat.** It could also explain why people often need to be supported in order to trigger a successful diet.

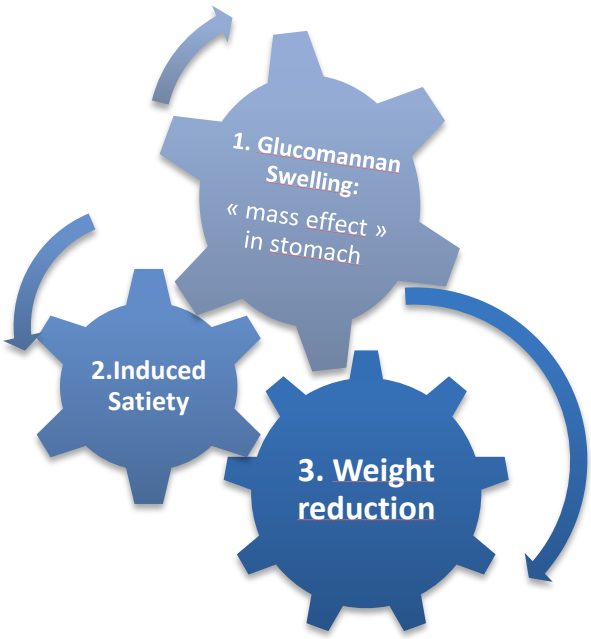


Figure 14: Glucomannan's main mechanisms of action. Glucomannan swells in the stomach by absorbing water in the gastric content, delays gastric emptying, induces satiety and thus contributes to the decrease of the hunger feeling which helps to control food intake; and hence contributes to the reduction of body weight.

As explained above, glucomannan is a soluble fiber that is not absorbed by the body. Several mechanisms have been proposed to explain the role of glucomannan intake on body-weight management.

4.4.1 Mechanical properties: swelling capacity

As mentioned previously, glucomannan forms a highly viscous, gel-like mass in the stomach when hydrated by absorbing water, forming a "mass effect"(Keithley *et* Swanson, 2005; Koroskenyi, 2001). Glucomannan solutions have an exceptionally high viscosity. As an example, 1% solutions of glucomannan are about 10-fold more viscous than comparable solutions of guar gum, and over a hundred-fold more viscous than pectin solutions. The viscosity of a newly made 1% solution develops gradually, rising to over 10 000 Centipoise (CPS) (equivalent to millipascals per second) after an hour and reaching a peak at about 5 hours (at least 50 000 cps) (McCarty, 2002).

Native konjac exhibits unusually high water absorbency, near 100 grams of water per gram of konjac (Koroskenyi, 2001). To illustrate, one gram of Glucomannan will absorb approximately one hundred milliliters of water in vitro (Walsh *et al.,* 1984).Thanks to these mechanical properties glucomannan has beneficial effects on the satiety sensation.

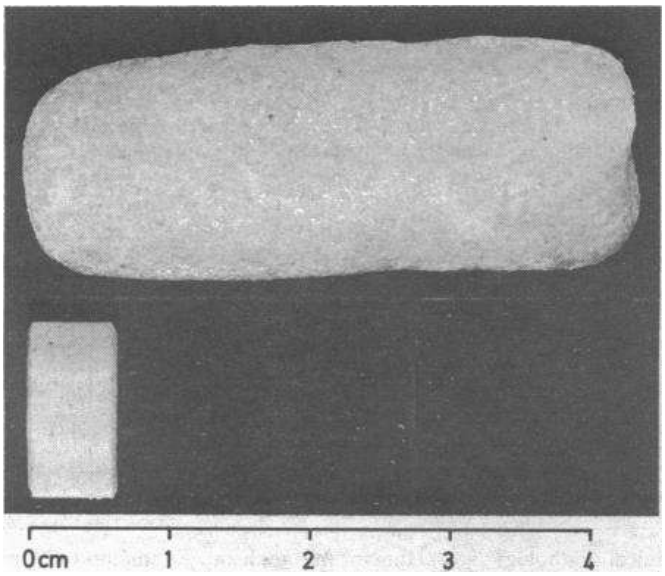


Figure 15: The volume of a bar of glucomannan, before and after immersion in water for 10 minutes (Henry et al., 1986).

4.4.2 Satiety promotion

Glucomannan's "mass effect" could **delay gastric emptying** and induce satiety (Keithley *et* Swanson, 2005).

In addition, by absorbing large quantities of water and by forming gels, glucomannan may further increase **stomach distention**. Stomach distension is suggested to trigger afferent vagal signals of fullness and hence contribute to satiety during meals and satiation in the post meal period (Howarth *et al.*, 2001). Satiety promotion leads to a decrease in subsequent energy intake (Keithley *et* Swanson, 2005).

4.4.3 Slowed absorption of fats and sugars

Glucomannan's viscosity, when in contact with water, could also slow down the absorption of fats and sugars, thus reduce the calories brought by food intake (Gallaher *et al*., 2000). By slowing down the absorption of carbohydrates, glucomannan could moderate postprandial insulin surges thus possibly improving diabetic control, and lowering LDL cholesterol (McCarty, 2002).

To sum up the data above, the following figure represents a simplified view of glucomannan's mechanisms:

To conclude, glucomannan can help during a weight loss diet by decreasing hunger feelings leading to a lesser food intake.

4.5 Proofs of efficacy and clinical efficacy of glucomannan on weight loss

Thanks to its mechanical properties and its capacity to induce a satiety sensation after absorption (as seen previously), glucomannan supplementation is an interesting way to support a weight loss diet. Indeed the weight loss property of glucomannan has been recognized by EFSA (European Food Safety Authority). The following biological property has been granted under the article 13.1 Health Claim:

- **Glucomannan contributes to the reduction of body weight in the context of an energy-restricted diet**
- Condition of use: at least 3 gram of glucomannan should be consumed daily in three doses of at least 1 grams each, together with 1-2 glasses of water before a meal, in the context of an energy-restricted diet (EFSA Journal 2010).

In weighing the evidence, the EFSA Panel (composed of scientific experts) took into account the intervention studies, which were of adequate sample size and duration. The panel found a **statistically significant effect of glucomannan on body weight loss in the context of a hypo-caloric diet when administered as a pre-load before meals, and that the mechanism by which glucomannan could exert the claimed effect is established,** as seen previously.

A total of 45 references were cited for the scientific substantiation of this claim. Among them, six reported on intervention studies in humans investigating the effects of glucomannan on body weight (Birketvedt *et al*, 2005; Cairella *et* Marchini, 1995; Vido, 1993; Vita, 1992; Vuksan, 1999; Walsh *et al.,* 1984). Also, the EFSA Panel identified three additional references cited in relation to other claims on glucomannan as being pertinent to this claim : Wood, 2007; Chen, 2003; Vuksan, 2001(EFSA Journal, 2010;8(10):1798)

The main objective of this study was to evaluate the weight reducing effect of a glucomannan fiber supplement in overweight subjects.

A randomized placebo controlled clinical study conducted by Grethe Støa Birketvedt from the Laboratory of Gastroenterology, Institute of Clinical Medicine, University of Tromsø, in Norway, on one hundred and seventy six men and women, showed that glucomannan, at a daily dose of at least 1.24 grams, taken for five weeks in the context of an energy-reduced diet (1,200 kcal per day) **induced body weight reduction in healthy overweight subjects.**

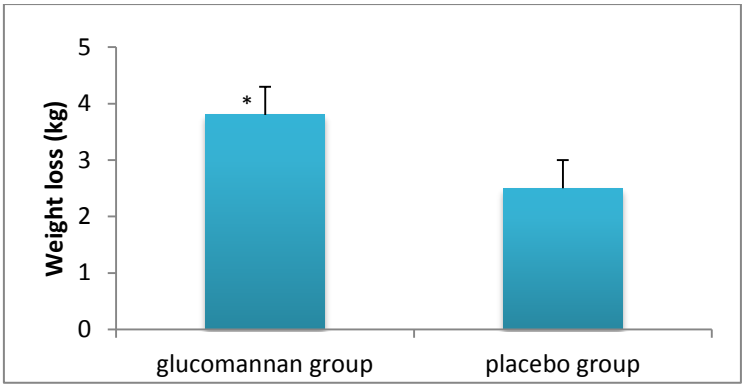


Figure 16: Changes in body weight during the treatment. Significant weight reduction compared to the control group: The glucomannan group lost 3.8±0.9 kg which is significant compared to the placebo group who lost 2.5±0.5 kg, *p<0.01 (Birketvedt *et al.,* 2005).

The study also showed that the addition of guar gum and alginate to glucomannan did not seem to cause additional loss of weight (Birketvedt *et al.*, 2005).

In the double blind placebo controlled, randomized trial, conducted by Cairella *et* Marchini, the authors notably studied the behavior of body weight, hunger and satiety sensation in 30 overweight women (BMI 25-30 kg/m²) treated for 60 days with a 1.200 kcal (5040 kj) diet plus either placebo or glucomannan. 4 grams of glucomannan, or placebo, were administered per day in capsule form with one to two glasses of water, 30-60 minutes before the two main meals.

All the variables considered show that **the low-calorie diet plus glucomannan is more effective than the low-calorie diet alone** (Cairella *et* Marchini, 1995).

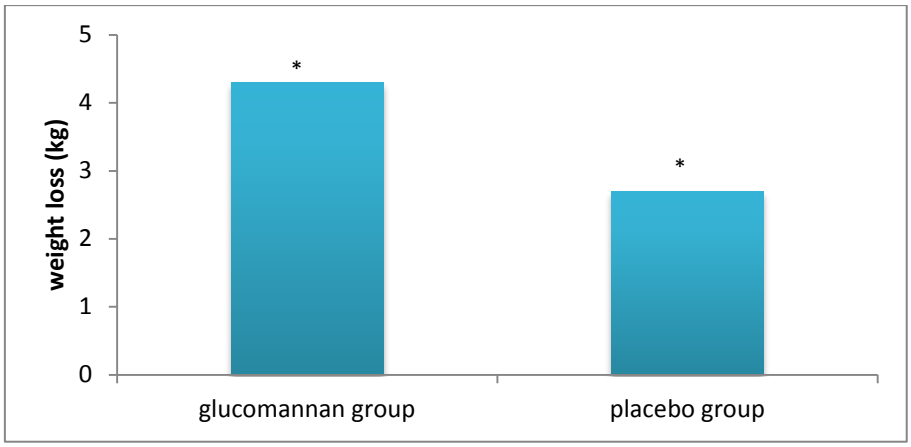


Figure 17: **Increased weight loss in overweight women supplemented with glucomannan vs. control group.** Body weight loss during the study was statistically significantly (*p=0.0017) higher in the glucomannan group (-4.3 kg) than in the placebo group (-2.7 kg, mean difference 1.6 kg, 95%CI=0.7-2.5) (Cairella et Marchini, 1995).

Another double-blind placebo-controlled, randomized clinical trial, including 20 patients with body weight 20% over their ideal, was conducted with either 3 g of glucomannan or of a placebo per day, with 240 ml of water one hour before each meal, for 8 weeks. The patients were advised not to change their eating or exercising habits. The report suggests **significantly greater weight loss in the treatment group than in the placebo group.** There were **no adverse events** in the treatment group (Walsh *et al.,* 1984).

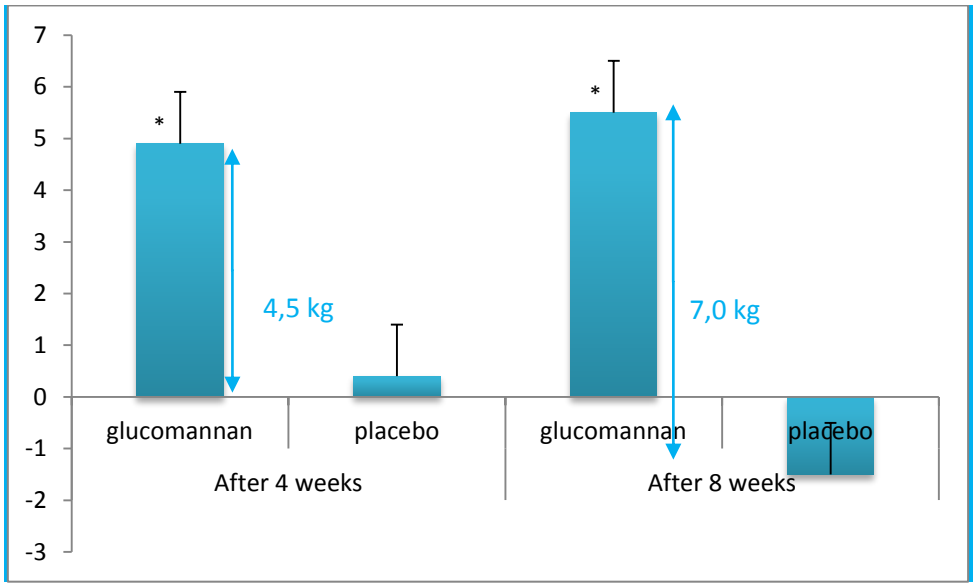


Figure 18: Increased weight loss in overweight women supplemented with glucomannan vs. control group after 4 and 8 weeks, p<0.005 vs placebo (Walsh *et al*., 1984).

In addition, many patients in this study indicated that they had a "full" feeling after taking glucomannan. Observations of satiety were made occasionally in patient interviews, but no complete survey was done.

4.6 Recommendations and dosage

Konjac glucomannan should be taken before each main meal or when snacking with a large glass of water at a dose of 3 grams per day.

Before advising this product, it is recommended that the pharmacist assures that the patient does not have abdominal pain or has not had digestive occlusions in the past.

A dose of 3g of glucomannan per day enables the use the **EFSA Health Claim 13.1 "Glucomannan contributes to the reduction of body weight in the context of an energy-restricted diet**"

4.7 Side effects and toxicity

There are a limited number of studies evaluating the short term security and tolerability of glucomannan intake. Due to the few data available and its history of use for over 1000 years, glucomannan seems to be well tolerated (Salas-Salvado *et al.*, 2007).

The side effects frequently reported after glucomannan intake at doses as low as 500mg, include **gastrointestinal disorders such as soft feces, diarrhea, flatulence, and abdominal pain**. These effects can be lowered or avoided by gradually introducing glucomannan into one's diet. The fermentation of the fiber in the colon by microflora bacteria is accompanied by the production of gas which can distend the intestine, causing pain. In addition, glucomannan can act as a laxative, and should not be used in the case of preexisting abdominal pain (Cottin, 2011; Gonzalez-Canga *et al.,* 2004).

More serious **intestinal or esophageal obstructions** have been observed after the intake of glucomannan capsule as doses as low as 500mg (Canga *et al.,* 2004; Salas-Salvado *et al.*, 2007).After similar cases of suffocation in children who consumed sweets containing glucomannan, the FDA emitted a warning as to the consumption of such products. Due to the risk of suffocation, the use of E425 konjac in jellified sweets has been prohibited in the European Union (Cottin, 2011).

4.8 Interactions

Even though soluble fibers can reduce the absorption of certain drugs such as contraceptives, they do not change the quantity absorbed (Garcia *et al.,* 2000)

4.9 Contraindication

Glucomannan should not be taken in the case of occlusion of the digestive tract (Keithley *et* Swanson, 2005).

4.10 Conclusion on glucomannan

To conclude, satiety increasing dietary supplements, such as glucomannan are also known as appetite moderators. They can help overweight or obese individuals with big appetites who wish to reduce their food intake. They have a mechanical action by absorbing large quantities of water once in the stomach and thus inducing satiety. Glucomannan supplements should be taken before each main meal with a large glass of water at a dose of 3 grams per day (one gram three times per day). Before advising this product, it is recommended that the pharmacist assures that the patient does not have abdominal pain or has not had digestive occlusions in the past. In order to obtain a weight loss effect, glucomannan supplements should always be associated with a healthy low calorie diet and regular exercise. They should never be used alone and by no means can replace a healthy diet. The majority of studies show a significant effect of glucomannan in weight loss in overweight individuals, notably when accompanied with a reduced calorie diet.

5. Conclusion on weight management dietary supplements

Many weight loss supplements and active ingredients exist which can become confusing for the consumer. They often represent a certain budget and their efficiency and safety should be looked into and advised by a doctor or pharmacist before purchase. It is also important to respect the doses recommended by health professionals and beware of medical interactions or contra-indications.

A number of factors affect research results associated with the efficacy of weight-loss supplements, such as small sample sizes, short intervention periods, little or no follow-up, and whether the supplement is given in combination with an energy-restricted diet or increased physical activity. The efficacy of supplements containing glucomannan and green tea at sufficient doses is supported by scientific evidence, as seen previously in this thesis.

There is no strong research evidence indicating that a specific supplement will produce significant weight loss (>2 kg), especially in the long term. Some foods or supplements such

as green tea, and fiber supplements may complement a healthy lifestyle to produce small weight losses or prevent weight gain over time. Thus, weight loss supplements are mainly intended for slightly overweight to overweight subjects. When taken alone, without a low calorie diet and increased physical activity, their efficiency can be poor. To conclude, these supplements are an aide and must be taken along with improved dietary habits, a healthy low calorie diet and exercise in order to obtain significant weight loss.

CONCLUSION

This thesis explores a broad spectrum of non-prescription options available to consumers who wish to lose weight. The conclusions that can be drawn from this document are numerous. Firstly, it can be noted that we live in a society dictated by the importance self-image and having a slim perfect body. Unfortunately the images that surround us do not correspond to real life. In publicities, over 95% of individuals have a BMI corresponding to a person who is normal or underweight; when in the "real life" in Europe 55% of adults are overweight of obese. The duality between the reality and the ideal image of men and women is very pronounced, and feeds the weight loss industry. Given the elements studied in this thesis, one can draw the conclusion that often, it can be more beneficial for a slightly overweight individual to stabilize his or her weight rather than try to lose weight by any means. Indeed, numerous weight loss strategies exist, not all healthy, efficient or even safe in the long run. It seems that the best way to lose weight or to stop gaining weight is to put into place healthy eating habits and regular physical activity. A weight loss diet should be individualized, adapted to each person's life style, health background, psychological context, culture, behavioral context and avoid drastic habit changes or exclusions of food categories. It should also be supervised by a qualified professional.

In order to boost the effect of this strategy, dieting strategies and dietary supplement are often put forwards. This thesis particularly studied two well known dieting methods and two active ingredients commonly found in dietary supplements. The hyper-protein Dukan diet generally leads to rapid weight loss but can have serious side effects such as rebound weight gain or kidney damage in the long run. The Weight Watchers method, which teaches healthy eating habits, encourages putting into place a long-term balanced and healthy life style but is costly and does not provide medical surveillance. Certain weight loss dietary supplements can lead to the loss of a couple kilograms when taken alone or more significant weight loss if taken at sufficiently high doses for sufficient lengths of time. Not all active ingredients lead to significant results. Two particularly interesting active ingredients are glucommannan and green tea. Glucomannan induces satiety by forming a viscous network in the stomach and inducing a full feeling, helping reduce food intake. Green tea increases the basal metabolism, leading the body to consume more calories thus modifying the energetic balance and favoring weight loss. When taken at correct doses and if the contra-indications are respected, certain dietary supplements can help potentiate the weight loss effects of a healthy low calorie diet. Dietary supplements are an aide for weight loss but will never replace the efficiency of a healthy low calorie diet followed along with an exercise program in order to stabilize or lose weight.

Lastly it is one of the pharmacist's roles to help orient and advise patients, according to their health context, in their choice of weight loss methods and dietary supplements, so don't hesitate to ask!

LIST OF FIGURES

BIBLIOGRAPHY

1) AFSSA. Avis de l'Agence française de sécurité sanitaire des aliments sur un projet d'arrêté relatif à l'emploi de substances à but nutritionnel ou physiologique et de plantes et préparations de plantes dans la fabrication de compléments alimentaires. Saisine n° 2007-SA-0231 du 8 septembre 2008, 8.

2) AFSSA. Risques et bénéfices pour la santé des acides gras trans apporté par l'alimentation. Avril 2005,1-6.

3) AFFSA-saisine n°2006-SA-0156. Avis de l'agence franciase de securité sanitaire des aliments relatif a l'évolution de la securité d'emploi d'un ingredient à base d'acides linoléiques conjugues (cla) dans les complements alimentaires, produits laitiers et jus d'orange. 23 mars 2007, 35.

4) Albright AL *et* Stern JS. Adipose tissue. In: Encyclopedia of Sports Medicine and Science, T.D. Fahey (Editor).1998. Internet Society for Sport Science: [On line] Available at <http://www.sportsci.org/encyc/adipose/adipose.html>. (Consulted on October 2, 2012).

5) Althuis MD, Jordan NE, Ludington EA, Wittes JT. Glucose and insulin responses to dietary chromium supplements: a meta-analysis. Am J Clin Nutr., 2002, 76 ,148–155.

6) Arrêté du 9 mai 2006 relatif aux nutriments pouvant être employés dans la fabrication des compléments alimentaires (J.O.n°123 du 28 mai 2006, 7977).

7) Auvichayapat P, Prapochanung M, Tunkamnerdthai O, Sripanidkulchai BO, Auvichayapat N, Thinkhamrop B, Kunhasura S, Wongpratoom S, Sinawat S, *et al*. Effectiveness of green tea on weight reduction in obese Thais: a randomized, controlled trial. Physiol Behav., 2008, 93, 486–91.

8) Bacci PA *et* Leibaschoff G, Physiopathology of cellulite. Basic and Clinical Dermatology, 200, 36, 41-74.

9) Backhed F, Ding H, Wang T, Hooper LV, Koh GY, Nagy A,et al. The gut microbiota as an environmental factor that regulates fat storage. 2004. Science's STKE, 101, 1571-8.

10) Berita Perawat Indonesia. Types of obesity- Are you an apple or a pear? 2010 [On line] Available at <http://1.bp.blogspot.com/_gQbLhYQDz7U/TGebV9Jk_DI/AAAAAAAADgE/gsga4aFYEso/s1600/android+gynoid+obesity.jpg>. (Consulted on October 3, 2012).

11) Bertrand C. Les compléments alimentaires amincissants: réglementation et efficacité. Analyse du thé vert, de l'acide linoléique conjugué, du chitosan, du chrome, de la reine des prés ; des pectines. Thèse d'Exercice de Pharmacie. Lyon : Université Lyon 1, 2011, 170.

12) Bérubé-Parent S, Pelletier C, Doré J, Tremblay A.Effects of encapsulated green tea and Guarana extracts containing a mixture of epigallocatechin-3-gallate and caffeine on 24 h energy expenditure and fat oxidation in men, 2005, 94, 3, 432-6.

13) Binnert C *et* Tappy L. Physiopathologie de l'obésité. Nutrition Clinique et Métabolisme, 2001, 15, 3, 194-197.

14) Birketvedt GS, Shimshi M, Erling T, Florholmen. Experiences with three different fiber supplements in weight reduction. J. Med Sci Monit., 2005, 11, 1, 5-18.

15) Blachère A. Prise en charge nutritionnelle, médicamenteuse et chirurgicale de l'obésité: rôle conseil du pharmacien. Thèse d'Exercice de Pharmacie. Clermont Ferrand : Université de Clermont I, 2010, 100.

16) Bose M, Lambert JD, Ju J, Reuhl KR, Shapses SA , Yang CS. The Major Green Tea Polyphenol, (−)-Epigallocatechin-3-Gallate, Inhibits Obesity, Metabolic Syndrome, and Fatty Liver Disease in High-Fat–Fed Mice, J Nutr., 2008, 138, 9, 1677–1683.

17) Brass EP. Supplemental carnitine and exercise. Review. Am J Clin Nutr., 2000, 72, 618-623.

18) Brent RL, Christian MS, Diener RM. Evaluation of the Reproductive and Developmental Risks of Caffeine. Birth Defects Res B Dev Reprod Toxicol., 2011, 92, 2, 152–187.

19) Brownell KD *et* Rodin J. Medical, metabolic, and psychological effects of weight cycling. Arch Intern Med., 1994, 154, 12, 1325-30.

20) Cairella M *et* Marchini G. [Evaluation of the action of glucomannan on metabolic parameters and on the sensation of satiation in overweight and obese patients]. Clin Ter., 1995, 146, 4, 269-74.

21) Canga G, Martínez F, Sahagún AM, Vieitez G, J.J.a, Liébana D, Pardo C, Robles C, Vega S, Glucomannan: Properties and therapeutic applications, [Glucomanano: Propiedades y aplicaciones terapéuticas] Nutricion Hospitalaria, 2004, 19, 1, 45-50.

22) Cani PD *et* Delzenne NM. The role of the gut microbiota in energy metabolism and metabolic disease. Curr Pharm Des., 2009, 15, 13, 1546-58.

23) Carnell S, Gibson C, Benson L, Ochner CN, Geliebter A. Neuroimaging and obesity: current knowledge and future directions. Obes Rev., 2012, 13, 43-56.

24) Chevallier L. 60 Ordonnances Alimentaires, 2e édition, Issy-les-Moulineaux, Editions Masson, 2011, 350.

25) Ciangura C, Touizer E, Basdevant A. Who is considered obese? Why? Clinical and therapeutic implications. J Visc Surg., 2010, 147.

26) Collectif. Weight Watchers, le guide des courses. Paris, Editions Gueblez, 1999, 298.

27) Collectif. The plaisir de maigrir Weight Watchers. Paris, Editions livre de poche, 2004, 288.

28) Complete well being solutions. Thyroid_files. [On line] available at <http://completewellbeingsolutions.com/thyroid_files/image001.gif>. (Consulted on October 2, 2012).

29) Connective Tissue: Adipocytes. The Histology Guide, Faculty of Biological Sciences, University of Leeds. [On line] Available at <http://www.histology.leeds.ac.uk/tissue_types/connective/connective_adipocyte.php>. (Consulted October 2, 2012).

30) Cotte A. *et* Duret A. Le chrome trivalent: intérêts et limites des supplémentations. Thèse d'Exercice de Pharmacie. Grenoble : Faculté de Pharmacie de Grenoble, 2010, 14.

31) Cottin S. Les compléments alimentaires amincissants : réglementation, efficacité et niveau de preuve de la caféine, de la L-carnitine, du glucomannane, de l'orthosiphon, et des probiotiques. Etude critique de compléments alimentaires. Thèse d'Exercice de Pharmacie. Lyon : Université Lyon 1, 2011, 184.

32) Curatolo PW *et* Robertson D. The health consequences of caffeine. Ann Intern Med., 1983, 98, 641-53.

33) Cynoder L *et* Fricker J. La vérité sur les compléments alimentaires. Paris, Odile Jacob, 2010.

34) Das UN. Obesity: genes, brain, gut, and environment. Nutrition. 2010, 26, 459-473.

35) Davis A, Fried T, Vasapollo L. Tea, Its Process, and The African Diaspora. [On line] Available at <http://mcdanielcoffeeteachocolate.wordpress.com/category/tea/>. (Consulted on January 5th 2013).

36) Décret n°2006-352 du 20 mars 2006 relatif aux compléments alimentaires (J.O. n°72 du 25 mars 2006, 4543).

37) Diepvens K, Westerterp KR, Westerterp-Plantenga MS. Obesity and thermogenesis related to the consumption of caffeine, ephedrine, capsaicin, and green tea. Am J

Physiol Regul Integr Comp Physiol., 2007, 292, 77-85.

38) Diepvens K, Kovacs EM, Nijs IM, Vogels N, Westerterp-Plantenga MS. Effect of green tea on resting energy expenditure and substrate oxidation during weight loss in overweight females. Br J Nutr., 2005, 94, 1026-34.

39) Dukan Diet Official Site: Weight Loss Experts. [On line] Available at <www.dukandiet.co.uk/>(Consulted on January 18, 2013).

40) Dubois J. La peau, de la santé à la beauté. Toulouse, Editions Privat, 2007, 208.

41) Dulloo AG, Duret C, Rohrer D, Girardier L, Mensi N, Fathi M, Chantre P, Vandermander J. Efficacy of green tea extract rich in catechin polyphenols and caffeine in increasing 24-h energy expenditure and fat oxidation in humans. Am. J. Clin. Nutr., 1999, 70, 1040-45.

42) Dulloo AG, Seydoux J, Girardier L, Chantre P, Vandermander J. Green tea and thermogenesis : interaction between cathechin-polyphenols, caffeine and sympathetic activity. Int J Obes Relat Metab Disord., 2000, 24, 2, 252-8.

43) Dunnick JK, Kissling G, Gerken DK, Vallant MA, Nyska A. Cardiotoxicity of Ma Huang/Caffeine or Ephedrine/Caffeine in a Rodent Model System. Toxicol Pathol., 2007, 35, 5, 657–664.

44) EFSA. Chromium picolinate, zinc picolinate and zinc picolinate dehydrate added for nutritional purposes in food supplements. Scientific Opinion of the Panel on Food Additives and Nutrient Sources added to Food. The EFSA Journal, 2009, 1113, 1-41.

45) Fatty acid metabolism. Structure and Development of Meat Animals and Poultry. Pages 116-120. [On line] Available at <http://www.bing.com/images/search?q=lipogenesis&view=detail&id=B625B03FB9AE49BF630E41F54C65F1A4B345C66E>. (Consulted on October 9, 2012).

46) Fernandez ML. Soluble fiber and nondigestible carbohydrate effects on plasma lipids and cardiovascular risk. 2001. Current Opinion in Lipidology, 2001, 12, 1, 35-40.

47) Fernandez-Real JM, Broch M, Vendrell J, Ricart W. Insulin resistance, inflammation, and serum fatty acid composition. Diabetes Care, 2003, 26, 1362-1368.

48) Franchi J, Pellicier F, André P, Schnebert S. The adipocyte in the history of slimming agents. Pathol Biol., 2003, 51, 5, 244-7.

49) Frayn KN, Humphreys SM, Coppack SW. Fuel selection in white adipose tissue. Proc Nutr Soc., 1995, 54, 177–189.

50) Fritsch H *et* Kühnel W. Atlas de poche d'anatomie, tome 2: Les vicères. Paris, Edition Médecine-Sciences Flammarion, 2003, 419.

51) Furuyashiki T, Nagayasu H, Aoki Y, Bessho H, Hashimoto T, Kanazawa K, Ashida H. Tea catechin suppresses adipocyte differentiation accompanied by down-regulation of PPARgamma2 and C/EBPalpha in 3T3-L1 Cells. Biosci Biotechnol Biochem., 2004, 68, 11, 2353-9.

52) Gallaher CM, Munion J, Hesslink R Jr, Wise J, Gallaher DD. Cholesterol reduction by glucomannan and chitosan is mediated by changes in cholesterol absorption and bile acid and fat excretion in rats. J Nutr., 2000, 130, 11, 2753-9.

53) García JJ, Fernández N, Diez MJ, Sahagún A, González A, Alonso ML, Prieto C, Calle AP, Sierra M. Influence of two dietary fibers in the oral bioavailability and other pharmacokinetic parameters of ethinyloestradiol. Contraception, 2000, 62, 5, 253-7.

54) Gassia V, Grognard C, Michaud T, Dermatologie esthétique, Du concept à L'exercice professionnel. Rueil-Malmaison, Editions Arnette, 2007, 195.

55) Giugliano D, Ceriello A, Esposito K. The effects of diet on inflammation: emphasis on the metabolic syndrome. J Am Coll Cardiol., 2006, 48, 677-685.

56) Girard P, De la minceur à l'anorexie, jusqu'où aller dans l'image que l'on donne de soi ?. Thèse d'exercice de Pharmacie. Nantes : Université de Nantes, 2011, Nantes, 137.

57) Golden EB, Lam PY, Kardosh A, Gaffney KJ, Cadenas E, Louie SG, Petasis NA, Chen TC, Schönthal AH. Green tea polyphenols block the anticancer effects of bortezomib and other boronic acid-based proteasome inhibitors. Blood, 2009, 113, 23, 5927-37.

58) Golubnitschaja O *et* Yeghiazaryan K. Opinion controversy to chromium picolinate therapy's safety and efficacy: ignoring 'anecdotes' of case reports or recognising individual risks and new guidelines urgency to introduce innovation by predictive diagnostics? EPMA J., 2012, 3, 1, 11.

59) Grove KA *et* Lambert JD. Laboratory, Epidemiological, and Human Intervention Studies Show That Tea (Camellia sinensis) May Be Useful in the Prevention of ObesityJ Nutr., 2010, 140, 3, 446–453.

60) Guh DP, Zhang W, Bansback N, Amarsi Z, Birmingham CL, Anis AH. The incidence of co-morbidities related to obesity and overweight: A systematic review and meta-analysis. BMC Public Health, 2009, 9, 88.

61) Hajer RH, van Haeften TW, Visseren FLJ. Adipose tissue dysfunction in obesity,

diabetes, and vascular diseases. European heart journal, 2008, 29, 2959-2971.

62) Heckman MA, Weil J, Gonzalez de Mejia E. Caffeine (1, 3, 7-trimethylxanthine) in foods: a comprehensive review on consumption, functionality, safety, and regulatory matters. J Food Sci., 2010, 75, 3, 77-87.

63) Hellstrom PM, Geliebter A, Naslund E, Schmidt PT, Yahav EK, Hashim SA, and Yeomans MR. Peripheral and central signals in the control of eating in normal, obese and binge-eating human subjects. Br J Nutr., 2004, 92, 1, 47-57.

64) Henry DA, Mitchell AS, Aylward, Fung MT, McEwen J, Rohan A. Glucomannan and risk of oesophageal obstruction. Br Med J. (Clin Res Ed), 1986, 292, 6520, 591–592.

65) Heymsfield SB, Thomas D, Nguyen AM, Peng JZ, Martin C, Shen W. Voluntary weight loss: systematic review of early phase body composition changes. Obes Rev., 2011, 12, 348-361.

66) Hooper LV, Midtvedt T, Gordon J. How host-microbial interactions shape the nutrient environment of the mammalian intestine. Annu. Rev. Nutr., 2002, 22, 283–307.

67) Horvath EM, Tackett L, McCarthy AM, Raman P Brozinick JT, Elmendorf JS. Antidiabetogenic effects of chromium mitigate hyperinsulinemia-industed cellular insulin resistance via correction of plasma membrane cholesterol imbalance. Mol Endochrinol., 2008, 22, 937-50.

68) Houille Lepigeon G. Obesité et surpoids: la solution des régimes allégés?. Pharmacie. Nantes. Université de Nantes, Faculté de Pharmacie, 2012, 164.

69) Howarth NC, Saltzman E, Roberts SB. Dietary fiber and weight regulation. Nutr Rev., 2001, 59, 5, 129-39.

70) Hughes LA, Arts IC, Ambergen T, Brants HA, Dagnelie PC, Goldbohm RA, van den Brandt PA, Weijenberg MP. Higher dietary flavone, flavonol, and catechin intakes are associated with less of an increase in BMI over time in women: a longitudinal analysis from the Netherlands Cohort Study. Am J Clin Nutr., 2008, 88, 1341–52.

71) Hursel R, Viechtbauer W, Westerterp-Plantenga MS. The effects of green tea on weight loss and weight maintenance, a meta-analysis. Int J Obes., 2009, 33, 956–61.

72) International Diabetes Federation. The IDF Consensus Worldwide Definition of the Metabolic Syndrome. International Diabetes Federation, 2006.

73) International Occupational Safety and Health Information Centre (CIS): Caffeine,

International Occupational Safety and Health Information Centre (CIS). [On line] Available at <http://www.ilo.org/dyn/icsc/showcard.display?p_lang=en&p_card_id=0405> (Consulted on November 15, 2012).

74) INVS, Situation et évolution des apports alimentaires de la population en France, 1997-2003, Paris, ed Labrador, 2005, 100.

75) Karhunen L, Lyly M, Lapveteläinen A, Kolehmainen M, Laaksonen DE, Lähteenmäki L, Poutanen K. Psychobehavioural factors are more strongly associated with successful weight management than predetermined satiety effect or other characteristics of diet. J Obes., 2012, 2740-8.

76) Keithley J *et* Swanson B. Glucomannan and obesity: a critical review. Altern Ther Health Med., 2005, 11, 30-4.

77) Kierszenbaum L. Histologie et biologie cellulaire. Bruxelles, Editions De Boeck, 2006, 618.

78) Klok MD, Jakobsdottir S, Drent ML. The role of leptin and ghrelin in the regulation of food intake and body weight in humans: a review. Obes Rev., 2007, 8, 1, 21-34.

79) Kotzki S, Saviuc P, CTV de Grenoble. Thé vert : étude rétrospective des cas recensés dans les CAPTV entre 2000 et 2010. Comite de coordination de toxicovigilance. 2010, 28.

80) Kovacs EM, Lejeune MP, Nijs I, Westerterp-Plantenga MS. Effects of green tea on weight maintenance after body-weight loss. Br J Nutr 2004, 91, 3, 431–437.

81) Kumar MNVR, Muzzarelli RAA; Muzzarelli C, Sashiwa H, Domb AJ. Chitosan chemistry and pharmaceutical perspectives. Chem. Rev., 2004, 104, 6017–6084.

82) Le Barzic M. Aspects psycologiques de l'obesité. Encyclopédie médic-chirurgical d'endocrinologie-Nutrition, Paris, Editions Elsevier, 2010.

83) Leon D, Algasahz JL, Rutz MA, Martin M. Chronic caffeine or theophylline intake during pregnancy inhibits A1 receptor function in the rat brain. Neuroscience, 2005, 131, 481–489.

84) Leon D, Albasanz JL, Ruiz MA. Effect of chronic gestational treatment with caffeine or theophylline on Group I metabotropic glutamate receptors in maternal and fetal brain. J Neurochem., 2005b, 94, 440–451.

85) Ley RE, Backhed F, Turnbaugh P, Lozupone CA, Knight RD, Gordon JI. Obesity alters gut microbial ecology. Proc Natl Acad Sci U S A., 2005, 102, 11070-11075.

86) Ley RE, Turnbaugh PJ, Klein S, Gordon JI. Microbial ecology: human gut microbes

associated with obesity. Nature, 2006, 444, 1022-1023.

87) Manach C, Williamson G, Morand C, Scalbert A, Rémésy C. Bioavailability and bioefficacy of polyphenols in humans. Review of 97 bioavailability studies. Am J Clin Nutr., 2005, 81, 230-242.

88) McCarty MF. Glucomannan minimizes the postprandial insulin surge: a potential adjuvant for hepatothermic therapy. Medical Hypotheses, 2002, 58, 6, 487-490.

89) Marti A, Moreno-Aliaga MJ, Hebebrand J, Martinez JA. Genes, lifestyles and obesity. International Journal of Obesity, 2004, 28, 29–36.

90) Martin A. Apports nutritionnels conseillés pour la population française. Paris, Tech&Doc, 3 édition, 2001, 99-102.

91) Melissopoulos A, Levacher C. La peau, structure et physiologie. Condé-sur-Noireau, Editions Tech & Doc Lavoisier, 1998, 152.

92) Mertz W. Chromium research from a distance: from 1959 to 1980. J Am Coll Nutr., 1998, 17, 6, 544-7.

93) Meynadier J. Précis de Physiologie cutanée. Paris, Editions de la porte verte, 1989, 291.

94) Mooradian AD, Failla M, Hoogwerf B, Marynuik M, Wylie-Rosett J. Selected vitamins and minerals in diabetes. Diabetes Care, 1994, 17, 464–79.

95) Mozaffarian D, Hao T, Rimm EB, Willett WC, Hu FB. Changes in diet and lifestyle and long-term weight gain in women and men. N Engl J Med., 2011, 364, 25, 2392-404.

96) Myers JL *et* Allen JC. Nutrition and Inflammation: Insights on Dietary Pattern, Obesity, and Asthma. American Journal of Lifestyle Medicine, 2012, 6, 14.

97) Nagao T, Hase T, Tokimitsu I. A green tea extract high in catechins reduces body fat and cardiovascular risks in humans. Obesity, 2007, 15, 1473–83.

98) Nagao T, Meguro S, Hase T, Otsuka K, Komikado M, Tokimitsu I, Yamamoto T, Yamamoto K. A catechin-rich beverage improves obesity and blood glucose control in patients with type 2 diabetes. Obesity, 2009, 17, 310.

99) Newby PK, Tucker KL, Wolk A. Risk of overweight and obesity among semivegetarian, lactovegetarian, and vegan women. 2005. Am J Clin Nutr., 81, 6, 1267-74.

100) NHS choises. Top 10 diets review. 20/12/2011.[On line] Available at <http://www.nhs.uk/Livewell/loseweight/Pages/top-10-most-popular-diets-

review.aspx>. (Consulted on January 18, 2012).

101) Ollier C. Minceur et Phytothérapie. Le Moniteur des Pharmacies. Cahiers II du 2393 du 7 avril 2001.

102) Padwal RS *et* Majumdar SR. Drug treatments for obesity: orlistat, sibutramine, and rimonabant. Lancet, 2007, 369, 9555, 71–77.

103) Pharmacopée Française Xème edition. Caféine. Pharmacopée Française Xème edition, Paris, Maisonneuve S. A. ed., 1986.

104) Pharmacopée Fraçaise. Reine des prés. Pharmacopée Fraçaise, Xème éd., 1986.

105) Pichon P. Régimes… Un marché en surpoids? Sunset presse, March 22, 2012. [On line] Available at <http://www.dailymotion.com/video/xplr8a_regimes-un-marche-en-surpoids_news>. (Consulted on September 7th 2012).

106) Pinna. Obesity caused by viral infections. [Dr.Pinna]. 2010. [On line] Available at <http://drpinna.com/obesity-caused-by-viral-infections-8280>. (Consulted October 2, 2012).

107) Pi-Sunyer FX. Epidemiology of Obesity and Weight Gain: The Impact on Diabetes. [On line] Available at <http://img.medscape.com/slide/migrated/editorial/cmecircle/2002/2049/pisunyer/slide14.gif >. (Consulted on October 3, 2012).

108) Pittler MH *et* Ernst E. Dietary supplements for body-weight reduction: a systematic review. Am J Clin Nutr., 2004, 79, 529–36.

109) PR Newswire Europe. Weight Management Industry is Expected Reach USD 216.1 Billion by 2015: Transparency Market Research. NEW YORK, 2012 published by transparency-market-research. [On line] Available at <http://en.youscribe.com/catalogue/press-and-journals/current-affairs-and-social-debate/media/europe-weight-management-industry-is-expected-reach-usd-216-1-billion-1826252> (Consulted on October 30 2012).

110) Rasmussen SE, Frederiksen H, Struntze Krogholm K, Poulsen L. Dietary proanthocyanidins: Occurrence, dietary intake, bioavailability, and protection against cardiovascular disease. Mol. Nutr. Food Res., 2005, 49, 159-74.

111) Reis JP, Loria CM, Steffen LM, Zhou X, van Horn L, Siscovick DS, Jacobs DR, Carr JJ. Coffee, Decaffeinated Coffee, Caffeine, and Tea Consumption in Young Adulthood and Atherosclerosis Later in Life: The CARDIA Study. Arterioscler Thromb Vasc Biol., 2010, 30, 10, 2059–2066.

112) Richard D, Monge-Roffarello B, Chechi K, Labbé SM, Turcotte EE. Control and Physiological Determinants of Sympathetically Mediated Brown Adipose Tissue Thermogenesis. Front Endocrinol., 2012, 3, 36.

113) Rideout TC, Harding SV, Jones PJH, Fan MZ. Guar gum and similar soluble fibers in the regulation of cholesterol metabolism: Current understandings and future research priorities. Vasc Health Risk Manag., 2008, 4, 5, 1023–1033.

114) Rumpler W, Seale J, Clevidence B, Judd J, Wiley E, Yamamoto S, Komatsu T, Sawaki T, Ishikura Y, Hosoda K. Oolong tea increases metabolic rate of fat oxidation in men. J. Nutr., 2001, 131, 11, 2848-52.

115) Rodriguez MS *et* Alberto LE. Interaction between Chitosan and oil under stomach and duodenal digestive chemical conditions. In Biosci Biotechnol Biochem., 2005.

116) Salas-Salvado J, Farres X, Luque X. Effect of two doses of a mixture of soluble fibres on body weight and metabolic variables in overweight or obese patients: a randomised trial. British journal of nutrition, 2007, 99, 1380-1387.

117) Scientific Committee on Food. Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Trivalent Chromium, Brussels – Belgium: European commission, health & consumer protection directorate-general, 2003, 18.

118) Scientific Opinion on the substantiation of health claims related to konjac mannan (glucomannan) and reduction of body weight (ID 854, 1556, 3725), reduction of post-prandial glycaemic responses (ID 1559), maintenance of normal blood glucose concentrations (ID 835, 3724), maintenance of normal (fasting) blood concentrations of triglycerides (ID 3217), maintenance of normal blood cholesterol concentrations (ID 3100, 3217), maintenance of normal bowel function (ID 834, 1557, 3901) and decreasing potentially pathogenic gastro-intestinal microorganisms (ID 1558) pursuant to Article 13(1) of Regulation (EC) No 1924/20061; EFSA Journal 2010, 8, 10, 1798.

119) Sherwood, Physiologie humaine, 2e edition. Editions de Boeck Université, 2006, 629.

120) Shi D, Nikodijevic O, Jacobson KA, Daly JW. Chronic caffeine alters the density of adenosine, adrenergic, cholinergic, GABA and serotonin receptors and calcium channels in mouse brain. Cell Mol Neurobiol., 1993, 13, 247–261.

121) Smith HS *et* Steinmaus CM. Health Effects of Arsenic and Chromium in Drinking Water: Recent Human Findings. Annu Rev Public Health., 2009, 30, 107–122.

122) Stearns DM, Silveira SM, Wolf KK, Luke AM. Chromium(III) tris(picolinate) is mutagenic at the hypoxanthine (guanine) phosphoribosyltransferase locus in Chinese hamster ovary cells. Mutat Res., 2002, 15, 513, 135-42.

123) Trevisanato S. Tea and Health. Nutrition reviews, 2000, 58, 1, 1-10.

124) Van Dam RM. Coffee consumption and coronary heart disease: paradoxical effects on biological risk factors versus disease incidence. Clin Chem., 2008, 54, 9, 1418-20.

125) Vaughan RA, Garcia-Smith R, Bisoffi M, Conn CA, Trujillo KA. Conjugated linoleic acid or omega 3 fatty acids increase mitochondrial biosynthesis and metabolism in skeletal muscle cells. Lipids Health Dis. 2012, 11, 142.

126) Vidal. Le guide des plantes qui soignent. 1ère éd. Issy-les-Moulineaux : Vidal, 2010, 466

127) Vincent JB. Recent advances in the nutritional biochemistry of trivalent chromium. Proc Nutr Soc., 2004, 63, 41-7.

128) Wada M, Nishimura Y, Watanabe Y, Takita T, Innami S. Accelerating effect of chitosan intake on urinary calcium excretion by rats. Biosci. Biotechnol. Biochem., 1997, 61, 7, 1206-1208.

129) Wall BT, Stephens FB, Constantin-Teodosiu D, Marimuthu K, Macdonald IA and Greenhaff PL. Chronic oral ingestion of L-carnitine and carbohydrate increases muscle carnitine content and alters muscle fuel metabolism during exercise in humans. J Physiol., 2011, 589, 4, 963–973.

130) Walsh DE, Yaghoubian V, Behforooz A. Effect of glucomannan on obese patients: a clinical study. Int J Obes., 1984, 8, 289–93.

131) Wang Y, Beydoun MA, Liang L, Caballero B, Kumanyika SK. Will all Americans become overweight or obese? Estimating the progression and cost of the US obesity epidemic. Obesity, 2008, 16, 10, 2323-30.

132) Webster's Revised Unabridged Dictionary, published 1913 by C. & G. Merriam Co. [On line] Available at < http://www.thefreedictionary.com/Phlogosis>. (Consulted on October 10th 2012).

133) Westerterp-Plantenga MS. Green tea catechins, caffeine and body-weight regulation. Physiol Behav., 2010, 100, 1, 42-6.

134) Westerterp-Plantenga MS, Lejeune MP, Kovacs EM. Body weight loss and weight maintenance in relation to habitual caffeine intake and green tea supplementation. Obes Res., 2005, 13, 1195–204.

135) WHO, 1997: World Health Organization (WHO). Obesity: preventing and managing the global epidemic. Report of a WHO Consultation on Obesity, 1997.

136) WHO, 2000 : WHO. Obesity: preventing and managing the global epidemic. WHO Technical Report Series number 894. Geneva: WHO, 2000.

137) WHO, 2012 a: Nutrition. Facts and figures. Overweight and obesity in adults. [On line] Available at <http://www.euro.who.int/en/what-we-do/health-topics/disease-prevention/nutrition/facts-and-figures>. (Consulted on August 28th, 2012).

138) WHO, 2012 b: Obesity and overweight, fact sheet n°311, 2012. [On line] Available at </www.WHO.int:mediacentre/factsheets/fs311/en/>. (Consulted on May 30th 2012).

139) WHO, 2012 c: A healthy lifestyle, Nutrition. [On line] Available at <http://www.euro.who.int/en/what-we-do/health-topics/disease-prevention/nutrition/a-healthy-lifestyle>. (Consulted on September 27, 2012).

140) WHO, 2013: BMI classification. BMI classification. [On line] Available at <http://apps.who.int/bmi/index.jsp?introPage=intro_3.html>. (Consulted on January 21, 2013).

141) Wood R. J, Effects of a carbohydrate-restricted diet with and without supplemental soluble fiber on plasma low-density lipoprotein cholesterol and other clinical markers of cardiovascular risk, Metabolism Clinical and Experimental, 2007, 56, 58– 67.

142) Wu CH, Lu FH, Chang CS, Chang TC, Wang RH, Chang CJ. Relationship among habitual tea consumption, percent body fat, and body fat distribution. Obes Res., 2003, 11, 9, 1088-95.

143) Xiao J *et* Yang W. Weight loss is still an essential intervention in obesity and its complications: a review. Journal of Obesity, 2012, 2012, 369-97.

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[Weight loss support: study of overweight, dieting and dietary supplement containing slimming active ingredients: case of green tea and glucomannan]

Résumé de la thèse :

Le surpoids et l'obésité sont des préoccupations de santé publique au niveau mondial. La culture de la minceur et la peur d'une pandémie de l'obésité, toutes deux martelées par les médias et par la société elle-même, sont très fortes dans toutes les catégories socioprofessionnelles. De très nombreuses stratégies de perte de poids sont disponibles pour le grand public. Cette thèse a pour vocation d'aider les pharmaciens et les patients à mieux comprendre les enjeux du surpoids. Son objectif principal est d'expliquer les méthodes de pertes et de maitrise de poids disponibles sans ordonnance médicale. Une attention particulière sera portée sur les principes actifs trouvés dans les compléments alimentaires minceurs, notamment le thé vert et le glucomannane.

Summary :

[Overweight and obesity are central health preoccupations worldwide. The media and social pressure to be thin as well as the fear of an obesity epidemic affect men and women of all ages and socio-professional categories. Many weight loss strategies are available to the general public. This thesis is a review of the overall non-prescription weight loss strategies that are available and is intended to help pharmacists and patients to better understand overweight and obesity as well as the most well-known weight loss options available. Specific attention will be brought to ingredients commonly found in weight loss dietary supplements, notably green tea and glucomannan because it is essential that pharmacist clearly understand the products they recommend to their patients.]

MOTS CLÉS: SURPOIDS, REGIME, COMPLEMENT ALIMENTAIRE, THE VERT, GLUCOMANNAN

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