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 REVIEW ARTICLE

Functional Food to Regulate Satiety and Energy Intake in Human

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Abstract: Nowadays obesity is affecting people from all socioeconomic levels in most of the countries worldwide. Appetite and satiety are complex processes which influence the energy regulation. As a solution to enable individuals to control their body weight, functional foods were developed in order to reduce the energy intake. However, the methodology to assess the satiating efficiency of functional foods, including monitoring through biomarkers, is very complex and needs to be standardized. The aim of the present work was to analyse the results published in the area of functional food and satiety to demonstrate the potential satiating role of these foods.

Keywords: Functional food, Healthy ingredients, Intake regulation, Satiety determination, Satiety biomarkers.

INTRODUCTION

Nowadays, the research on the regulation of food intake in human is on the rise, considered as the main focus to understand a possible cause of the high prevalence of obesity and non-transmissible chronic diseases in the global population. A great number of countries showed obesity prevalence higher than 10% [1, 2] and it is evident that the prognostic is not promissory for the obesity and other chronic diseases associated with obesity [3, 4]. The actual life style, characterized by the consumption of high energy density foods and a low level of physical activity in several populations, is the main cause of these health problems. The main result of this obesogenic behavior is a positive energy balance which represents the basis of the major prevalence of overweight and obesity. Furthermore in several studies, conducted on low income families, the consumption of high carbohydrates and low dietary fiber diet was demonstrated [5, 6]. This kind of diet, determines a rapid enzymatic digestion, increasing glycemia levels and inducing a low satiety [7, 8]. At the same time the low amount of dietary fiber is associated with a poor weight management [9, 10]. A possible dietary solution to control the obesity rate is to recommend the intake of common foods with high satiety potential. In the last years functional foods which include ingredients with a high potential to produce a strong feeling of fullness were developed. The efficacy of these foods must be evaluated by clinical trials performed in humans and accepted by regulatory organisms (Halford Jc, 2012). The importance of these foods in the actual population feeding is essential to control the energy regulation process. This latter regulation is based on complex biological events between the peripheral gastrointestinal tissues and the central nervous system, which integrates the information and controls the process. Also the energy regulation is affected by the environmental factors [11]. For these reasons, the methodological designs and the procedures applied to study the efficacy of functional foods in the energy intake regulation, represent essential factors for industrial, consumer and scientist sectors. The aim of the present work was to analyse the results published in the area of food and satiety to demonstrate the potential satiating food. This information is valuable to provide a background for the discussion of conceptual and practical alternatives considered in the development of functional foods.

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Energy Intake Regulation

The models proposed to study the regulation of energy intake indicate that food intake starts with external signals related to their metabolism (Fig. 1). The food intake begins when glycaemia falls and plasma fatty acid concentration increases [12], as demonstrated by Campfield and co-workers which found, in their study conducted on rat, that food intake starts when glycaemia falls near 12% [13]. On the other side, the increment of satiety is due to an elevation of plasma cholecystokinin (CCK) and insulin in the central nervous system. Both biomarkers are associated to the surfeit condition [14]. During the consumption phase, food intake is controlled by orosensoriales, cognitive and postingestive effects [15, 16]. Term phase is led primarily by the food volume in the stomach and by the chemical composition in the small intestine [17 - 19]. The food frequency consumption is another important factor in the food intake regulation, because it is highly related to the cell energy status. The feeding frequency increases when cells are in energy deficit [20]. From a physiological perspective, the biochemical reactions originate signals captured by the central nervous system, leading to the sensation of appetite or fullness recognized by the subjects. However, the selection of foods and the amount of energy consumed by individuals are strongly conditioned by dietary factors. For example, the culinary processes and the palatability are involved in energy regulation [21]. In addition it is well established that other nutritional variables such as energy density, macronutrient content and variety of foods offered during a meal time, can modulate energy intake [22 - 24].

	FEEDING PHASE		
	INITIAL	CONSUMPTION	TERM
Internal stimulus related to ¬ metabolism	Slight drop in plasma glucose		Increase CCK levels
	Increase fatty acid levels		Increase Insulin levels
Food related Stimulus		Effects: Orosensorieles	Volume in the stomach
		Cognitive Postingestive	Chemical composition in the small intestine

Fig. (1). Model intake regulation.

The terms more used to identify the different biological state that express the energy regulation are appetite, satiation and satiety. Appetite can be defined as the internal state that produces a strong motivation to eat when foods are available. Once the individuals eat, some signals influence the ending of the feeding, giving a feeling of fullness and satiation [25, 26]. Each meal is followed by a variable time period characterized by the absence of hunger, defined as a state of repletion of energy that occurs after a meal [27]. The length of inter-meal period is known as satiating efficiency which is specific for each food or their combinations [28, 29]. The intake of foods with elevated satiety efficiency also decreases the number of eating episodes during the day, thus reducing food and energy intakes [30, 31]. The sequence of events shown in Fig. (1), explain the neural and hormonal responses in anabolic or catabolic pathways determining the energy balance and body weight changes [14, 32, 33]. Furthermore, the food intake regulation is influenced by multiple factors beside the biological factors such as psychological, socio demographic, cultural and individual factors [11, 34].

Methodology to Obtain Healthy Functional Foods to Regulate Energy Intake

The methodology approach applied in most of the researches on appetite and satiety is varied and complex because of the numerous variables involved [31, 35, 36]. Consequently, the results obtained from these studies are related with the experimental design applied and the derived conclusions have to be carefully interpreted. The methodologies used in most of the reviewed studies for the development and evaluation of functional foods, designed to increase satiety, are divided into three stages (Fig. 2). The first stage corresponds to "intervention activities" and consists mainly in the addition of bioactive compounds into the food matrix to obtain a new food that can be able of producing satiety and body weight regulation. At this stage it is necessary to define the functional ingredient, the dose and the selected vehicle food. The second stage corresponds to the evaluation of technological processes applied to obtain a functional food ready to be developed industrially. At this stage, it is necessary to handle technological functionality of the food to achieve high acceptability and sensory characteristics. The third stage is the application of a clinical methodology to evaluate the satiety potential of the functional food through various experimental designs.

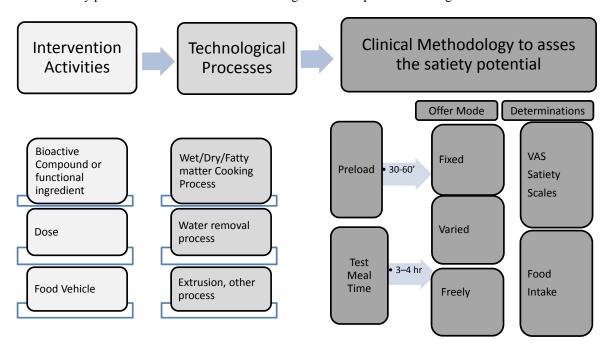


Fig. (2). Experimental design to develop and assess the efficacy of functional foods in satiation and satiety. The acronym VAS stand for Visual Analogue Scale.

One of the designs most frequently used to evaluate a short term satiety consists of the assignment of a preload test where subjects have to consume the whole of a small portion (100-150 g) [36]. After a brief period of time (30 or 60 minutes) the amount of food that subjects are able to eat is measured or the perception of satiety assessed using the Visual Analogue Scale (VAS) [37, 38]. This method is used to determine the short-term satiety: the participants are asked to specify their sensations of hunger, satiety, fullness, and desire to eat in a particular features, using this scale of values from 0 to 10 centimeters [39 - 41]. It is advisable to use the VAS before starting the trial, immediately before and after the consumption of the test food and at 15-30-60-90-120 minutes, to compare the results with the measurements of plasmatic biomarkers, such as glycemic response.

Another experimental design to assess the satiety potential of the functional food is to include it in a meal time, such as breakfast or lunch. After 3 hours, the satiety was evaluated determining the subsequent intake or using VAS [36]. In both designs, preload or meal time, foods are supplied in pre-weighed portions beyond the energy requirement of the subjects. Three ways to provide food are available: fixed, varied or freely. In the first case, a unique preparation in an amount greater than normally consumed are offered, with the possibility to give more to the subjects if requested. In the varied offer mode, 5 or 6 foods with different nutritional and orosensorial characteristics, such as a salad, a stew, a glass of juice or drink, a piece of bread, a serving of fruit and milk dessert are offered. Other authors prefer to use different types of sandwiches accompanied by portions of fruit and liquid foods. In the freely offer mode, the food is served on a table and the subjects could take as much as they liked. In this design a lot of small portions of several foods are

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offered, taking care to strike a balance between different sensory characteristics of sweet and savory foods, liquids, gels and solids foods, meat and vegetables, dairy products and baked goods. Total food intake is determined by differential weighing which compares the amount of foods offered and the amount left over by each subject [35]. There are many studies that only measure satiety by the VAS without the determination of the food intake in the subsequent meal. The three methodological stages described in the Fig. (2) can be applied to elaborate functional foods in the area of the regulation of energy intake. Nevertheless, in each stage it is important to constantly create a valuable feedback for the optimization of the whole process.

Methodological Design Considerations

In each stage of the experimental design it is necessary to take into account a large number of variables. For example, in the intervention stage it is necessary to essay different doses of the bioactive compound to obtain an adequate satiation and satiety potential and a good sensorial and technological quality in the functional food. The scientific literature shows that for the same bioactive compounds, clinical studies use different doses. Thus, there are studies that essayed elevated doses to assure the beneficial effect of the compound and others studies are interested in essaying a minor dose which can be found in normal food portions. It is necessary to control also the amount and the type of macronutrients, dietary fiber, phytochemical and other food compounds that could affect satiety and accompany functional ingredient studied. On the other hand, technological and culinary treatments influence satiating efficiency of foods. For example, the gelatinization of starches in cooking water drastically reduces their satiating effect [7, 42]. Additionally, physiochemical changes in food matrix such as texture, viscosity and consistency are detected when foods are industrially or culinary treated [43, 44]. Moreover, the sensorial characteristics of foods can also affect their ability to produce satiety. Some authors showed a correlation between brain activity in the regions that control food intake and the rate of pleasantness [45 - 47]. Consequently, the nutritional, sensorial and physiochemical characteristics of food must be paired or controlled and the results published frequently did not show an adequate control of the experimental variables. The various ways to offer food are appropriate for different: the fixed supply is suitable for subjects with small gastric capacity, like preschool children. Instead, offering varied or freely designs are more appropriate for adolescent and adults. In these latter two, the concept of sensory-specific satiety is used; it means that the subjects can obtain satiety for one type of feed, still maintaining an appetite for foods with different characteristics [48 - 50]. The variety of textures, tastes, smells and colors is also involved in this phenomenon [16, 33, 51]. During a meal, the absence of varied choice tends to limit food intake, whereas variety tends to promote eating. Therefore, in this design it is very important to get a good balance between the physiochemical, sensory and nutritional characteristics of food offered. In this way, subjects can express their real potential capacity to consume. Regardless, the three ways to offer food (fixed, varied or freely) should all include foods with high acceptability by the subjects involved in the study. Another important aspect to evaluate the satiating potential of a functional food or ingredient is to standardize the hunger level of each subject, regulating the fasting condition of the previous days. The time between the ingestion of functional food and the measurement of satiety change, basing on the purpose of the study. If the aim is to evaluate the effect of the oro-sensorial and gastrointestinal factors on satiety, the delay should be no more than 30 minutes, while if the purpose is to investigate the inhibitory effects post-absorptive, the delay must be longer.

The review of published studies shows that there are two methods used for satiety measurement. The first evaluates the perception of satiety reported by the participants and the second measures the actual food intake. Therefore, the VAS provides a subjective evaluation of satiety while the measurement of actual food intake provides an objective assessment. Both methods are widely accepted in satiety assessment and can be considered as markers to evaluate the direct effects of food intake [38]. Some variables that must be considered during a study are the environmental conditions in which results are obtained. The laboratory conditions are more appropriate to have an adequate control of the different variables while the free-living conditions are similar to the normal way of eating of the subjects. When the objective of the study is to obtain physiological responses or to study the conceptual framework of some biomarkers, the research must be carried out in a laboratory context. On the contrary, if the aim of the investigation is to determine the effect of food on body weight changes which requires a long period of time, it is more appropriate to perform the measurements in a free-living environment. In both approaches the environmental conditions need to be considered in their projection to the feeding of the individuals.

Metabolic Biomarkers Related to Satiety

The experimental researches in the field of energy regulation need to study different compounds derived from the metabolism of macronutrient or peptides in the cells, acting as messengers from the gastrointestinal tract to the central

nervous system, principally in certain regions of the hypothalamus. These biomarkers help to understand how the processes of satiety and appetite are modified by the dietary components, contributing to reach an optimum in the usefulness of the functional ingredients designed to increase satiety. The metabolic biomarkers are simultaneously determined with the measurement of satiety. These biomarkers may provide valuable information to explain the conceptual basis to understand the effect of dietary bioactive compounds on human cells. Some researchers recommend the determination of Cholecystokinin (CCK) and Glucagon-Like Peptide-1 (GLP1) as markers of satiation and the measure of glycaemia, insulinemia, Gastric Inhibitory Polypeptide (GIP) and Peptide YY (PYY) as biomarkers of satiety [52]. Ghrelin is an excellent marker of satiety, which acts on hypothalamus receptors as a peripheral hormone, stimulating the expression of neuropeptide Y and agouti-related protein [53]. The ghrelin's relation with hunger responses and food intake is well established [54 - 56]. In a study conducted by Batterham and co-workers the role of PYY on satiety was assessed. The research demonstrated that PYY is a biomarker of satiety acting as a peripheral signal on central nervous system receptors [57].

Carbohydrates are the nutrients mainly consumed in the diet and consequently they are important in the regulation of energy intake, to have biomarkers able to predict the effect of carbohydrate intakes on satiety. Postprandial glucose and insulin levels depend on the available amounts of carbohydrates and on their digestion rate. If during the digestion, the carbohydrates are rapidly absorbed, the glycemic response is rapid and when an accentuate fall is produced, a higher energy intake was proven [58, 59]. Consequently sharp curves are associated with hunger and flat curves are associated with satiety [60, 61]. Furthermore, high glycemic response increases the risk of obesity, diabetes, cancer and cardiovascular disease [62]. Some investigators suggested that insulinemia is a more sensible biomarker than glycemic [63, 64]. The cereals and their products presented extremely different glycemic responses and in the low zones oat (*Avena sativa*) and the pasta cooked "al dente", that is cooked to be firm to the bite are located [65, 66]. On the other hand, white bread determines the increase of blood glucose which can be explained with the high concentration of starches with rapid digestion rate [67, 68].

Biomarkers for proteins are the levels of amino acid in plasma which are related to the release of hormones and peptides connected with the central nervous system [69]. The oxidation process of amino acids, that starts in the liver and facilitates ATP synthesis, is directly related with the protein concentration in foods consumed: this suggests that in order to obtain a potential rise of satiety, it's necessary to consume a high amount of dietary proteins in one meal per day [70, 71].

There are a considerable number of researches on metabolic biomarkers and their relationship with appetite and satiety in humans. However, their use in the assessment of food satiety efficiencies or in the contribution on the design and the evaluation of functional foods, are not completely accepted because the evidences are limited and controversial. The plasma levels of glucose and insulin are the more considered biomarkers used as valuable information to connect the theory with the practical actions in the area of functional foods. The analysis of the literature revised suggests that the majority of the experimental designs are carried out in a short period of time either in the same meal time (satiation) or in the subsequent meal time (satiety). These studies are planned to evaluate the physiological processes of appetite, satiety and satiation but they were not designed to evaluate the energy intake in the long term where it is possible to evaluate the changes in bodyweight. The validity of the metabolic biomarkers in the field of appetite and satiety is a key point to have an approximation of conceptual framework to explain how the cells respond to the metabolic and biochemical challenges induced by food intake and to give an answer to the question "why we eat the energy and foods that we eat?"

Most Promising Functional Foods to Increase Satiety According to Scientific Knowledge

A great proportion of functional foods for energy regulation is based on the addition of isolated soluble fiber (*i.e.* β -glucans) to the food matrices or the inclusion of foods rich in soluble fiber such as oats and barley (*Hordeum vulgare* L.). Most of the health benefits associated with high viscosity foods are due to β -glucans, which demonstrated some physiological effects such as the satiety and the moderation of the glycemic and insulinemic postprandial response [37, 72, 73]. To understand if the β -glucans benefits are dose-dependent, several studies were conducted to define the lowest dose which demonstrated the effect above mentioned. The incorporation of oat β -glucans (from 2.5 g to 5 g) into beverages with different energy contents, showed a higher perception of satiety compared to control food, but a dose-response relationship was not observed. Moreover, the oat had a high viscosity which produced the increased perception of satiety [74]. In the same way Beck et al, showed that a lower dose of oat β -glucan (2.2 g) was able to increase subjective satiety while an higher dose of 5 g of β -glucans reduced energy intake by more than 400 kJ in the subsequent

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meal [75]. The effect of foods combined with β -glucans in the population must be taken into account for the submission of healthy messages. Few studies linked the recurrent intake of oat β -glucans with the reduction of body weight. During a research of Beck *et al.*, fourteen overweight subjects (balanced by gender) were followed for 3 months with an energy restricted diets with different level of β -glucans. The use of the soluble fibre in food could be related to the weight loss and appetite control [76].

The literature revised in this paper showed that in short time and in laboratory conditions the addition of oat β -gucans are beneficial to increase satiety and to decrease the glycemic and the insulinemic responses. Barley is another cereal investigated as source of soluble dietary fibre with healthy benefices [77 - 80]. Crackers and cookies enriched with 3.5 g of barley β -glucans showed positive responses in the insulinemic response [81]. As demonstrated by Vitaglione *et al.*, this soluble fibre may be also incorporated into snack products such as biscuits, determining a decrease in appetite sensation [82]. In some researches some functional ingredients were incorporated into the white wheat bread with the aim to test the glycaemic and insulinemic responses and to evaluate the satiety capacity of the bread [83, 84]. In the study, Liljeberg showed that a bread with 80% barley produced a glycaemic index of 33 while the control bread presented a glycaemic index of 69 [83]. In the same way, Hallström found that bread products based on a novel wheat genotype with elevated amylose content (38%) induced significant lower postprandial glucose response [84].

Others wheat products such as pastes were also used as vehicles to add healthy ingredients such as soluble and insoluble fibres: β - glucans, resistant starches, FOS [85 - 88]. It is well established that proteins are the macronutrient that causes the greater satiety in the short-term [69, 89]. However, most of the studies were experimental designs which used protein concentrations at 45-50% of the total energy intake [71, 90]. Long-term studies are less conclusive and used diets providing 25-45% of energy from protein [91]. These results were applied to functional foods based on protein isolated such as casein, whey and soy protein [92, 93]. Actually, the research in this area is based on the effect of different food proteins types beyond their protein concentration [94]. This is the case of milk proteins such as casein and whey. The results demonstrated that both compounds increase satiety but with diverse efficiency. Casein presents a more rapid digestion in upper gastrointestinal zones and its metabolic action appears in a short postprandial time [95]. On the contrary, whey protein shows a more slow digestion and its metabolic role can be expressed in a longer time [96, 97] demonstrated that the whey proteins are more potent than casein in the increase of CCK and GLP 1 and in the decrease of appetite. Today, an important research area is to formulate and evaluate functional foods based on the combination of protein with soluble fiber with the purpose to obtain a synergism to have a product with a high satiating potential.

The experimental research on food intake and satiety is very important, in order to design, develop and evaluate the role of functional foods on population's health. The primary aim is low energy intake and maintaining body weight of individuals at the risk of obesity. Foods need to be carefully evaluated considering food chemical composition, the structure and the physical properties of the food matrix, processing conditions, the amount of the satiating ingredients and their interactions with the others food components. When these foods meet the requirements of the food regulation of each country, they can be incorporated in the market system in varied forms [98], facilitating the consumers purchase and representing a dietary tool to alleviate the epidemic of obesity in the whole world.

CONCLUSION

The present paper suggests some actions useful to obtain a better application of the different methodologies for the evaluation of the efficacy of functional foods in the increase of satiety. These actions are summarized in the following items:

- Development of studies to standardize the methodology for assessing appetite and satiety.
- Use of standard food used as controls to assure the validity of the methodologies.
- Work on the homologation of the health messages and nutrition labelling.
- Increase private and public budget to study the healthy characteristics of new ingredients added to functional foods.
- Increase the knowledge on the usefulness of biomarkers used in the design of functional foods.
- Provide scientific information about the use of functional foods to increase satiety and how they can be integrated in the diet of the consumers.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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