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Experiments Confirming the Food Restricting Properties of Jojoba

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Abstract

After the oil has been extracted from the jojoba nuts, the residual flour still contains about 30% of proteins. Therefore, it was investigated in the seventies and eighties if this flour could serve as a venerable food substitute for humans and/or animals in the semi-arid areas, comparable with soy in the oriental countries. However, animals showed severe growth retardation and research was stopped until later research revealed strong biological activities towards certain jojoba flour compounds.

In addition, control of food intake and weight gain of animals is also important but also in the world of animals control on food intake and weight gain is important. There are several applications in the meat industry where for eg. methods are needed to limit broiler breeder pullets in their food intake in order to avoid bone malformation, high mortality rates and excessive fat accumulation. A useful autonomous limitation of the food intake could be achieved by supplementation of 4% de-oiled jojoba flour to the standard ration of broiler breeder pullets. In addition, the supplementation of simmondsin to pet food will also be appreciated by the pet-owner not only for financial reasons, but because it will also increase the lifetime of his loyal companion.

Although an efficient food restriction without the feeling of hunger can be obtained, some of the observed negative effects should be taken seriously in consideration. The earlier described growth retardation and strong repression of the fertile capacities is NOT due to the food restricting properties of the dimethyl simmondsin but mainly to angiogenesis inhibiting properties of other simmondsin derivate present in jojoba flour. Whereas the food restricting properties have been exclusively attributed to Dimethyl simondsine, the angiogenesis inhibiting properties are induced by the desmethyl- and didesmethyl simmondsins (and their ferulates).

1- Introduction

After the oil has been extracted from the jojoba nuts, the residual flour still contains about 30% of proteins. Therefore, it was investigated in the seventies and eighties if this flour could serve as a venerable food substitute for humans and/or animals in the semi-arid areas, comparable with soy in the oriental countries. However, animals showed severe growth retardation and research was stopped until later research revealed strong biological activities towards certain jojoba flour compounds, which redirected the whole research on this subject.

2- Early experiments

2A- Jojoba flour thought to be toxic:

Young animals fed ad libitum with jojoba flour showed growth retardation (**Booth et al., 1974; Verbiscar et al., 1980; Ngou Ngoupayou et al., 1981; Ngou Ngoupayou et al., 1985; Manos et al., 1986**). Originally, it was believed that the jojoba plant was toxic because of the presence of simmondsin . It was stated that the -CN part would give rise to HCN in the body when digesting the simmondsin compound (**Booth et al., 1974;Verbiscar et al., 1980; Williams, 1980**), thus leading to emaciation. Meanwhile, it has been proven that digestion of simmondsin does not lead to liberation of cyanides into the body (**Cokelaere et al., 1992b**), but rats fed with 3% de-oiled jojoba flour still showed a lower weight gain than the pair-fed animals (**Cokelaere et al., 1993a**).

2B- Anti-trypsin factors:

The phenomenon of emaciation has also been attributed to the presence of the so-called 'anti-trypsin factors' (**Samac and Storey, 1981; Storey etal., 1982; Sanchez-Lucero and Price, 1988**). These toxic or better called non-eatable compounds are most probably p-coumaric polymeric acids and derivates which are present in the peel fragments in huge amounts thus causing a bitter taste. These compounds are water soluble bacteriostatic and likely to interfere with the intestinal flora. When using a universal oil extraction technique by expelling, a press cake is obtained from which these p-coumaric polymeric acids and derivates cannot be removed anymore. A refinement procedure for jojoba flour has been invented and patented (d'Oosterlynck) to eliminate the peel fragments out of the flour. (http://users.telenet.be/jojoba/patents.htm). This patented technique does not exclude the production of cold-pressed jojoba oil by expeller.

3- Food restriction

3A- Discovery of food restricting properties of jojoba flour:

De-oiled and refined jojoba flour contains ça. 5 to 7% dimethyl lsimmondsin and as much simmondsin derivates (Desmethylsimmondsin, Didesmethyl simmondsin and their

ferulates). This flour has still an inhibiting effect on the food intake (**Cokelaere et al.,1992a**). Pure dimethyl simmondsin does not affect taste since the same results were obtained with intra-gastric intubation and normal oral administration. The simmondsin aglycon obtained after treatment with galactosidase has the same activity on equimolar basis than the simmondsin -D-glucoside. Food intake inhibition by simmondsin is a result of cholecystokinin (CCK) stimulation, a peptide hormone with strong anorexigenic capacities (**Cooper and Dourisch, 1990**) which subsequently stimulates trypsin production from the pancreas (**Cokelaere et al., 1993a,b**). In consequence of this, proteolytic degradation is enhanced and the amount of spliced amino acids increases. A negative feedback system will then down regulate the food intake. The inhibiting effect on the food intake is dose-dependent; the more simmondsin present in the diet, the more the food intake will be reduced. Limiting the food intake by this way had no harmful consequences on adult organisms within certain limits. On the contrary, fast growing young organisms which do need a lot of protein at this moment, will encounter serious detrimental effects by this way of food deprivation. This explains partially the negative results obtained by most investigators in earlier studies (**Booth et al., 1974; Verbiscar et al., 1980; Manos et al., 1986**); they always performed experiments with fast growing young animals in combination with unrefined jojoba flour, usually in unappropriate high doses.

3B -The concept of Fasting:

The genetic and physiological constitution of animals and humans is the reflection of a long history of periods with food shortage (**Bray, 1999**).Individuals ate as much as they could to build up storage for worse periods. In addition and maybe as a consequence of this, most cultures during history of mankind have developed fasting periods which are commonly associated with purification rituals for the body. Nevertheless,during this long period of human evolution there was no selection pressure on genes responsible for satiation. Only recently (a.o. since the introduction of the potato and the development of non-perishable foods (freezed, vacuum-dried, canned etc…), there is a huge food surplus in the western countries and people are not readily adapted to it. The increased availability does not always result in satiation due to deficiencies in for eg. the leptin hormone or its receptor, finally leading to obesities

3C- Obesitas & leptin:

The Ob-gene (derived from obesitas) codes for the 16 KDa leptin protein and is mainly produced by adipocytes (**Hamann and Matthaei 1996;Trayhurn et al., 1999**). The Db gene codes for the leptin receptor (Ob-R)(Kielar et al., 1998), this receptor is functionally related to the interleukin-6 receptor which is a typical receptor for signal transduction. Either soluble or membrane-bound receptors are described (**Lollman et al.,1997**). The soluble forms are important for leptin transport through among others the

blood-brain barrier. Within the brain (**Campfield et al.,1996**) membrane-bound receptor types are present mainly at the plexus choroideus (a vascular network secreting cerebrospinal fluid) and on the hypothalamus (secreting several peptide hormones for stimulation of the thyroid, regulation of the food intake (**Leibowitz and Alexander, 1998**),drinking and sexual tempers (**Rohner-Jeanrenaud and Jeanrenaud, 1997**).

Scientific research has revealed an adipostate function for leptin levels in the body. The leptin level informs the body about its energy balance and fat storage. Changes in leptin concentration will result in a change of appetite and metabolic activity (**Schwartz and Seeley, 1997**). The more fat is stored, the more leptin will be produced which gives a signal in the brain to arrest eating and to increase basal metabolism (**Guerre-Millo,1997**). When fat storages are decreasing, leptin will also decrease by which the brain knows that the organism has to eat again and to lower the basal metabolism in order to save energy. There has also a connection been found between leptin and insulin; the latter which is released after the flour will increase the leptin concentration in order to down regulate the food intake. This system works with a closed feedback-loop: when the leptin concentration is too high it will down regulate the insulin secretion on its turn (**Fehmann et al., 1997**). The leptin/insulin balance can even be changed in function of the diet. Besides an effect of leptin on the appetite, it has also effects on hematopoiesis (**Sivan et al., 1997**), the basal metabolism via the thyroid (**Wolthers et al., 1997**) (See further) and on the reproduction. The magnitude of the fat reserve is influencing the fertility; when the % of body fat is either to high or to low infertility can be induced (see further). The leptin concentration has a direct effect on the leptin receptors that are present in the ovaries and placenta (**Spicer and Francisco, 1998**).

In some cases of obesities, the concentration of leptin is markedly increased; the addition of leptin is not beneficial in these cases of obesities. As a matter of fact, most obese people have not a problem with their leptin production but with their leptin receptor. A mutation in the leptin receptor can lead to an altered signal transduction (i.e. an altered sensitivity with respect to the leptin concentration). There are 2 interesting mouse models for this kind of research: the Ob/Ob (-/-) mouse which cannot produce leptin and the db/db (-/-) mouse which has no functional Ob-R leptin receptor (corresponding with the (fa/fa) Zucker rats). Supplementation of 0.25% simmondsin in the diet resulted in a food intake inhibition in both normal and (fa/fa) Zucker rats. Moreover, the (fa/fa) Zucker rats were more sensitive for the food intake reducing capacities of the simmondsine (**Flo et al., 1999**). Therefore, simmondsin shows also perspectives for obese people with an impaired leptin receptor function.

3D- Food restriction and the induction of Apoptosis:

Restricting the food intake markedly reduces the incidence of spontaneous and experimentally induced cancers (**Pashko and Schwartz,1992; Thurman et al., 1995**). Especially the reduction in calorie-rich food decreases the cell proliferation in general and inhibits cancer development (**Tessitore et al., 1996; Birt et al., 1999**). Tumor promoters induce an increase in cell replication and a decrease in apoptosis; hereby promoting tumor formation. Moreover, food restriction has the opposite effect (i.e. decreased cell replication and increased apoptosis), thus providing protection against carcinogenesis (**Bursch et al., 1994**).Complete food withdrawal for 8 days or food reduction by 40% for 3 months eliminated 20-30% of normal rat liver cells through apoptosis (**Grasl-Kraupp et al., 1994**). Preneoplastic cells showed besides a higher degree of DNA replication also a higher degree of apoptosis thus decreasing their number with 85%. The decreased amount of preneoplastic liver foci persisted throughout the following 17 months after return to ad libitum feeding although rates of cell replication and apoptosis were normalized rather quickly. The addition of nafenopin, a peroxisome proliferator and tumor promoter could only generate half as many hepatocellular adenomas and carcinomas as in animals fed unrestrictedly throughout their lifetime. In general, tumor promoters act as 'survival factors' by inhibiting apoptosis preferentially in preneoplastic and maligne cells thus leaving the chance to the tumor for further progression. On the other hand, factors which stimulate apoptosis and decrease cell replication will decrease the number of (pre)neoplastic cells (**Schulte-Hermann et al., 1997**). The last action can be obtained by a well considered food restriction. Using dimethyl simmondsin, a controlled food restriction up to 50% of the food intake is possible without the organism suffering hunger (Cokelaere)

3E- Caloric restriction and anti-aging:

At present, caloric restriction is believed to be the only way to protect mammalian species (humans included) against aging and age-related diseases through an appropriate low caloric diet (**Heydari et al., 1993 ;Randerath et al., 1991**). Doing so, live expectation should get increased substantially.Possible mechanisms conferring protection against aging through caloric restriction are thought to be a less quick decrease in heat shock protein Hsp70 (**Heydari et al., 1993**), an increased detoxification of free radicals (**Feuers et al., 1993**), a decreased loss of DNA methylation or an increased number of 'I' compounds (**Randerath et al., 1993**).

Since simmondsins do possess strong anorexigen properties (**Cokelaere etal., 1992b; Cokelaere et al., 1995**), a strong diet based on simmondsins or refined de-oiled jojoba flour resulting in caloric restriction could be imposed to an organism without causing the feeling of hunger. Since the food restricting properties of the simmondsins are dose dependent, the body could stay much longer free of all kind of aging diseases when

used in the optimal dose (i.e. the dose whereby optimal caloric restriction is obtained). Of course the reduced food has to be of adequate composition with respect to all necessary oligo-elements, vitamins and essential oils and amino-acids.

3E- Food restriction & fertility:

Although adult animals supplemented with simmondsin are slimmer than control animals, no other persistent harmful side effects have been found at present. However, this is only the case for adult individuals within certain constraints. Broiler breeder pullets showed serious impairment in their reproductive capacities when supplemented with 4% de-oiled jojoba flour during their growth faze starting from week 3 (**Vermaut et al.,1998a**). The percentage of jojoba flour had to be decreased further to 2.5% in order to keep the same weight as the group of chickens manually restricted from week 3 until week 20. Once maturation was achieved, animals treated with jojoba flour in their growth faze could not produce eggs due to a non-developed ovary; they subsequently died because they could not deposit their eggs. On the other hand, adult lay hens supplemented with 12% de-oiled jojoba flour could be forced to molting whereby regression of the oviduct was detected, but after withdrawal of the jojoba supplementation, the oviduct restored and the egg-laying improved markedly in the post-molting period. Jojoba flour had apparently no irreversible effect on the re-growth of the oviduct in adult hens (**Vermaut et al., 1998b**).

Furthermore, the experiments mentioned above were conducted with jojoba flour which was not refined correctly. In adult mice, reproduction ceased nearly immediately using 0.2% of pure simmondsin (i.e. free of any other 'toxic' compound), and fertility remained suppressed during the whole treatment period of 3 months **(Raes et al.,** in preparation).

Reproduction restarted after withdrawal of simmondsin; the first pregnancies were usually aborted or resulted in a reduced litter number (i.e. only 2 or 3 newborns which showed no visual aberrancies and showed normal fertility levels in their adult faze). After a few menstruation cycles, all mice regained normal fertility parameters. From a biochemical view, fetuses can be regarded by the mother individual as a tumor with respect to their protein and energy demand. In both cases a strange and spontaneously anarchistic reacting organism is withdrawing mainly proteins and energy from the host in order to assemble its own tissues. In case of food deprivation the quickly proliferating organism cannot maintain itself anymore, dies and will be resorbed by the host. We propose that this way of action can also be used to battle fast growing tumors.

Food deprivation also decreases the population of ovarian follicles in prepubertal rats (Lintern-Moore et al., 1981). A foetus develops and nourishes via the mother, and an inadequate diet may cause premature births, prenatal mortality or abortion (**Morgan, 1999**).

It is also well-known that anorexia may disrupt the menstruation cycle (**Golden et al., 1997**).

Fertility is influenced by the energy storage; therefore female suffering anorexia or obesitas are usually infertile.

However, the complete inhibition of reproduction could possibly evolve through another mechanism as well, eg. due to an inhibition of the mitosis or meiosis through a hormonal feedback. Food restriction will induce a higher apoptotic rate combined with a decreased rate of cell replication (**Bursch et al., 1994**). Humans and animals are still able to produce descendants although they are suffering chronic food deprivation and visual shortcomings (cfr. Ethiopia). Treatment of adult mice with simmondsin had a direct and absolute down regulating effect on the fertility with a minor effect on food deprivation and thus a neglecting effect on their weight loss (ça. 15%) compared to the untreated group (Raes et al., in preparation). This suggests an effect of simmondsin on the hormonal balance, either directly or indirectly. Maybe simmondsin could have also applications as a new anti-conception strategy which induces emaciation at the same time.

Once more, we have to state that simmondsin has no applications for fast growing or pregnant individuals at this moment.

3F- Influence of food restriction on thyroid hormone levels:

Increasing T4 (Thyroxin) induces increased basal metabolism, O2-consumption, body temperature, blood pressure and hypernervosity. The thyroid hormones have besides their effect on the general metabolism also an effect on cell differentiation and sexual maturation.

Simmondsin treatment (0.5%) in adult rats induces a reduction of the food intake by 40% and a lowering in the T3 (triiodo-thyronine) just like in the pair fed group (**Cokelaere et al., 1995**). The decrease in T3 would be the result of an increased T3-breakdown due to hepatic inner-ring iodinating (IRD) type I and III, since the T4 concentration remains usually unaffected (**Darras et al., 1995**). On the contrary, in fast growing rats (**Cokelaere et al., 1993a**) and pregnant rats (**Cokelaere et al., 1993c**), an increase in T3 can be observed. Protein deficiency in fast growing animals is known to lead to an increased T3 level (**Tulp et al., 1979**) which is not the case for adult animals (**Rostom de Mello et al., 1989**).Meanwhile, it has also been demonstrated that cell proliferation induced by T3 reduces formation of hepatocellular carcinoma's (**Ledda-Collumbanoet al., 1999**). At first sight, this is contradictory to the fact that agents that induce proliferation are usually carcinogenic and those that decrease cell proliferation in favor of apoptosis are considered to be protective against cancer. We have to remark here that T3 is an endogenous hormone. Tumors usually don't show any response anymore to signals from the organism since they are lacking intercellular gap junctional communication with normal cells (**Yamasaki et al.,**

1995), thus leaving the opportunity of the cancer cells to develop uninhibited. Most probably,cancer cells are not responsive anymore to T3 signaling too compared to normal cells. If this discrepancy would lead to a selective proliferation of the normal cells, cancer cells could also be deprived of energy and amino acids.

In conclusion we could say that extreme food reduction and/or protein shortage would give rise to plasma T3; thus providing us a mechanistic explanation why drastic food deprivation is protective against cancer. The observed growth retardation in fast growing animals (**Booth et al., 1974;Verbiscar et al., 1980; Ngou Ngoupayou et al., 1981; Ngou Ngoupayou et al., 1985; Manos et al., 1986**) could be the result of the changes in thyroid hormone levels as observed by **Cokelaere et al. (1993c)**.

4- Conclusion

4A- Advantages of simmondsin or refined jojoba flour usage in food restriction:

It is quite obvious that (western) people are looking for decennia after the ultimate emaciation product, since obesities is nowadays one of the major health risk factors. In addition, control of food intake and weight gain of animals is also important but also in the world of animals control on food intake and weight gain is important. There are several applications in the meat industry where for eg. methods are needed to limit broiler breeder pullets in their food intake in order to avoid bone malformation, high mortality rates and excessive fat accumulation (**Yu et al., 1992a,b**). For the time being ,manual food restriction is achieved by laborious intervention of the farmer using skip-a-day programs etc..., but these methods are seriously questioned by animal welfare organizations. A useful autonomous limitation of the food intake could be achieved by supplementation of 4% de-oiled jojoba flour to the standard ration of broiler breeder pullets (**Decuypere et al., 1994**). In addition, the supplementation of simmondsin to pet food will also be appreciated by the pet-owner not only for financial reasons, but because it will also increase the lifetime of his loyal companion.

4B- Restrictions in the use of simmondsin or refined jojoba flour:

Although an efficient food restriction without the feeling of hunger can be obtained, some of the observed negative effects should be taken seriously in consideration. The earlier described growth retardation and strong repression of the fertile capacities is NOT due to the food restricting properties of the dimethyl simmondsin but mainly to angiogenesis inhibiting properties of other simmondsin derivate present in jojoba flour. Whereas the food restricting properties have been exclusively attributed to Dimethyl simondsine, the angiogenesis inhibiting properties are induced by the desmethyl- and didesmethyl simmondsins (and their ferulates).

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