



Advantra Z®

Observations on its effects and mechanisms of action.

An extract of a Citrus fruit (normally *C. aurantium*) containing a family of indirect-acting adrenergic amines (β -sympathomimetics) that facilitate utilization of energy substrates, stimulate metabolic processes, favour uptake of amino acids into muscle, increase lipolysis and can exert mild hunger-suppressant effects.

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U.S. Patent 6,224,873: Regulation of appetite, body weight and athletic function with materials derived from citrus varieties

U.S. Patent 6,316,499: Methods for increasing the muscle mass of a human with materials derived from citrus varieties

U.S. Patent 6,340,481: Regulation of athletic function with materials derived from citrus varieties

U.S. Patent 6,340,482: Methods for inducing weight loss in a human with materials derived from Citrus varieties

Other domestic and offshore patents pending.

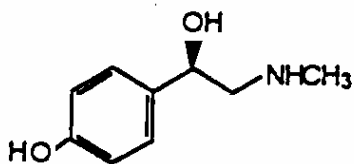
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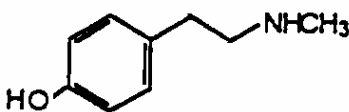
FORMAL STRUCTURE/FUNCTION STATEMENT:

BITTER ORANGE (CITRUS AURANTIUM) CONTAINS SMALL AMOUNTS OF ALKALOIDS SUCH AS SYNEPHRINE AND OCTOPAMINE, WHICH ARE DIRECT- AND INDIRECT-ACTING ADRENERGIC AGENTS. ADRENERGIC AGENTS WITH β -AGONIST ACTIVITY STIMULATE LIPOLYSIS AND INCREASE THE RESTING METABOLIC RATE IN SOME PERSONS, THUS INCREASING THE REMOVAL AND OXIDATION OF FAT FROM ADIPOSE TISSUE STORES. **THIS STATEMENT HAS NOT BEEN EVALUATED BY THE FOOD AND DRUG ADMINISTRATION. THIS PRODUCT IS NOT INTENDED TO DIAGNOSE, TREAT, CURE OR PREVENT ANY DISEASE.**

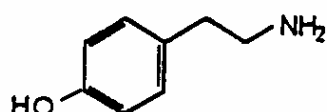
Advantra Z® is an extract of the Chinese herb zhi-shi (immature Bitter Orange; Citrus aurantium). The extract contains alkaloids which are related to the ephedrine alkaloids and have similar effects on metabolism and breakdown of fat, that is, they increase the metabolic rate, and they also increase the rate of breakdown of stored fat (lipolysis) in the body (Jones, 1998). The alkaloids present in Advantra Z® include synephrine, hordenine, octopamine, tyramine and N-methyltyramine.



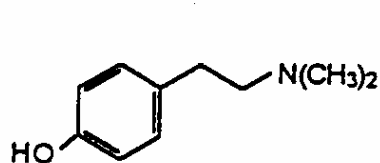
Synephrine



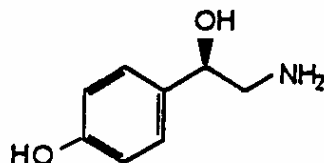
N-Methyltyramine



Tyramine



Hordenine



Octopamine

While foods and medicinal herbs derived from Citrus species have been used, and continue to be used, for a variety of food purposes and for their health benefits, they have not previously been identified as herbs or plants which have value in the treatment of weight problems or for improving physical performance and fitness. In part, this is due to the fact that levels of the active agents in most Citrus products are low; highest levels are found in parts of the plants that are not normally eaten, or in immature plants.

For example, levels of these agents in orange juice are expressed in parts per million, or even parts per billion. In practical terms, that means drinking 40 or more pints of orange juice per day, or eating 80 oranges, to get the intake of the active agents that would be obtained from one or two capsules, tablets or bars containing Advantra Z®.

The main adrenergic amines (alkaloids) of the citrus extract, Advantra Z®, are synephrine and N-methyltyramine, which act almost wholly indirectly and are active by mouth. Synephrine is used in medicine in Europe, but has been replaced in North America by ephedrine and pseudo-ephedrine. In classical tests, these citrus alkaloids show properties similar to ephedrine (Goodmore and Gilman, 1941), with activation of β -receptors (Munson, 1995). More recently, studies have shown that both octopamine and synephrine appear particularly effective in stimulating lipolysis (Carpene et al., 1999; Fontana et al., 2000), a postulated β_3 -receptor effect (Dulloo, 1993). Wenke et al. (1967) had previously revealed that synephrine was about 3.5 times as effective in stimulating lipolysis as octopamine. There are thus indications that the alkaloid mixture in Advantra Z® is superior to the mixture of ephedrine alkaloids in Ma-huang (*Ephedra sinica*) in terms of effects on β -receptors in general.

However, this theoretical superiority does not extend to the field of side effects. Initial studies in lean volunteers (Hedrei & Gougeon, 1997) and obese volunteers (Pathak & Gougeon, 1998), while showing excellent thermogenic responses, failed to reveal any evidence of increased heart rate, blood pressure or central nervous system stimulation. A clinical study reported by Colker et al. (1999) also demonstrated excellent effects on weight loss with a total absence of side effects.

Thus though the Citrus alkaloids appear to be at least as thermogenic as the ephedrine alkaloids, they are clearly gentler than the latter and do not cause the minor side effects associated with use of Ma-huang (nervousness, agitation, palpitations, increases in blood pressure). The better tolerance of the Citrus alkaloids is thought to be because they do not pass so readily into the brain, and may target fat cells rather more specifically.

The actions of Advantra Z® can therefore best be described as those characteristic of mild indirect-acting sympathicomimetic agents (also known as adrenergic agents), which usually elicit release of noradrenaline (norepinephrine) from presynaptic sites. This in turn activates both α - and β -adrenoceptors. In the case of the Advantra Z® alkaloids, however, there is evidence that dopamine is also released from the presynaptic sites (Hedrei & Gougeon, 1997); dopamine is present in these sites, but generally serves only as a precursor for noradrenaline. As far as noradrenaline is concerned, the perceived effects on different organs and tissues depend on the relative proportions of the two types of receptors, which mediate different responses. At a basal level, classical pharmacology teaches that α -activation results in contraction of smooth muscle (except for intestinal smooth muscle) while β -activation causes relaxation of smooth muscle and stimulation of the myocardium. But this picture is complicated by the fact that both α - and β -receptors can be subdivided into further types with differing distributions and sensitivities, and may be even further complicated by the possibility that sensitivities to dopamine may not parallel those for noradrenaline.

At a cellular level, activation of β -receptors results in stimulation of adenylate cyclase. This leads to increases in intracellular levels of cyclic adenosine monophosphate (cAMP), which, through a complicated mechanism, results in the observed reactions.

The β -receptors can also be further subdivided into β_1 , β_2 , and β_3 types, the last of which is strongly believed to be responsible for the lipolytic and thermogenic effects of adrenergic agents, while interactions with the other two types of β -receptors are known to control cardiac effects.

Effects on blood pressure, however, are in part due to the activation of α -receptors.

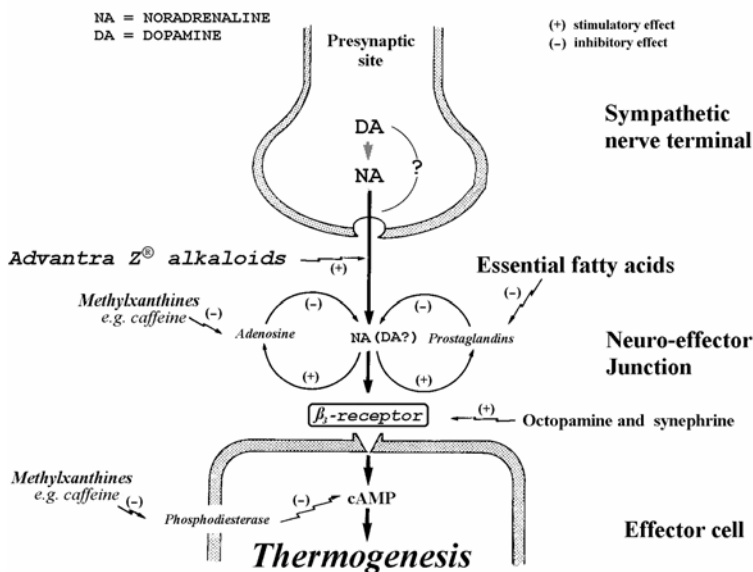
Central nervous system effects of adrenergic agents appear to depend on activation both α - and β -receptors (with the exception of β_3 -receptors). The multi-receptor response is also important in explaining observed synergistic effects of caffeine on certain actions of adrenergic agents.

The overall response to such agents, reflected in perceived effects, is governed by the distribution of receptors in terms of types and populations. As an example, the activation of β -receptors causes vasodilation of vessels in the heart and skeletal muscle while simultaneous α -activation results in vasoconstriction in other vascular beds. This is effectively the classical "fight or flight" response, which together with other metabolic results of adrenoceptor activation is intended to put the body into an optimal state for physical exertion.

The metabolic results of adrenoceptor activation also include effects on lipolysis and thermogenesis. In the case of lipolysis, activation of certain α -receptors inhibits the process, while activation of β_3 -receptors stimulates lipolysis and at same time, possibly in part due to increased availability of substrate, induces a thermogenic response. The overall response of the adipose tissue thus depends on the relative proportions of α - and β_3 -receptors. A high ratio would produce a comparatively lower thermogenic response than a low ratio. The diminishment of thermogenic response associated with the increasing proportion of α -receptors may explain why some studies of thermogenic responses to adrenergic activation identify two populations: responders and relative non-responders.

Though the above represents the generally accepted explanation of the actions of adrenergic agents, initial clinical observations with the Advantra Z[®] alkaloids have failed to reveal cardiovascular effects (increased pulse rate and blood pressure) or undue stimulation of the central nervous system, which would be typical of, for example, the ephedrine alkaloids from *Ephedra sinica* (Ma-huang). These observations do, however, show an obvious effect on thermogenesis (Hedrei and Gougeon, 1997; Pathak and Gougeon, 1998), with a concomitant effect on weight loss and a substantial stimulation of fat loss (Colker et al., 1999).

The lack of central nervous system effects can be attributed to the relatively low lipophilicity of the Citrus alkaloids, which will slow their passage across the blood-brain barrier. However, the absence of cardiovascular activity implies that the Advantra Z[®] alkaloids have little effect on α -, β_1 - and β_2 -receptors, while the thermogenic effect confirms that they do activate the peripheral β_3 -receptors.



Part of the explanation for this unusual dissociation may be found in the fact that Advantra Z[®] alkaloids appear to release dopamine and noradrenaline from the presynaptic sites, and that while there are satisfactory mechanisms for the re-uptake of noradrenaline, the dopamine released could remain longer in the synaptic gap, prolonging the activation of β_3 -receptors. It could be speculated that though dopamine is similar to noradrenaline in properties, it may differ in specificity and preference for β_3 -receptors.

However, recent studies have shown that both octopamine and synephrine, alkaloids in the extract, are β 3-receptor agonists in mammalian cells (Carpene et al., 1999; Fontana et al., 2000). Wenke et al. (1967) had previously demonstrated that octopamine had a significant lipolytic effect, but that synephrine was about 3.5 times as potent, also indicating that these components of Advantra Z[®] have high specificity for β 3-receptors.

Thus while there is some direct evidence from actual receptor studies that the Advantra Z[®] alkaloids (octopamine and synephrine) show specificity for β 3-receptors, the experimental evidence from studies in humans suggests strongly that this must indeed be one of the main mechanisms of action:

- In volunteers, no evidence of cardiovascular effects after single or repeated doses, but significant increases in metabolic rate.
- In obese subjects, significant increases in rates of weight loss, due almost entirely to fat loss (a consequence of lipolysis), but no evidence of any side effects or changes in cardiovascular parameters.

These observations indicate relative absence of effects on α -, β 1- and β 2-receptors, but a strong effect on β 3-receptors. It remains to be determined whether this is due to peripheral dopamine effects, is a possible consequence of disassociation of the actions of alkaloids in the mixture, or is a result of both the postulated mechanisms.

Increasing the metabolic rate is beneficial in weight loss, since the metabolism becomes sluggish in overweight and obese subjects placed on low calorie diets; by increasing the metabolic rate, weight loss is improved. Since the breakdown of stored fat is also increased, more of the weight lost comes from fat, and body protein from lean tissues is spared, thus helping prevent the loss of lean body mass that also often occurs during dieting.

While the actions of adrenergic agents that demonstrate good thermogenesis without significant cardiovascular and central nervous system effects make them ideal adjuncts for regulating and controlling weight problems, they can also be useful as ergogenic aids to improve physical performance (Yang and McElligott, 1989). The acute action is to increase energy availability and, thus, increase the capacity for physical exertion, while longer-term actions result in an increase in muscle mass, particularly when combined with appropriate diet programs and training. Indeed, it has been suggested that such agents may act as very effective anabolic agents when given over long periods of time. Both the beneficial ergogenic effects and the valuable effects on weight loss stem from the combination of the effects on lipolysis and the thermogenic effects. Thus by increasing the rate at which fat is released from body stores (lipolysis), while simultaneously increasing the metabolic rate (thermogenesis), the removal of unwanted fat stores is accelerated.

Since there is increased availability of substrates (the free fatty acids which are released from the fat stores) for oxidation, the body has access to greater amounts of energy. The body's use of these substrates spares protein that might otherwise be oxidized for energy. Used conjointly with a high protein intake and an exercise program, this can result in increased availability of amino acids for incorporation into protein in the muscle mass.

ANOTHER ASPECT OF THERMOGENESIS!

Since the main use of thermogenic agents is in aiding weight loss, it seems appropriate to speculate on the involvement of the eicosanoids in the mechanisms involved. It has been known for some time that rates of weight loss can be increased if intake of essential fatty acids (EFAs; precursors of the eicosanoids) is adequate; EFAs of the omega-6 and omega-3 families have been shown to increase thermogenesis. It is not known whether this is an intrinsic consequence of their mechanisms of action (as precursors for eicosanoids and as membrane constituents), or whether it merely represents the rectification of a pre-existent but unsuspected EFA deficiency. Goubern et al. (1990), for example, showed that brown adipose tissue cells recovered from EFA-deficient rats responded poorly to noradrenaline, but that addition of linoleic acid (omega-6 EFA) and the saturated fatty acid, palmitic acid, to the medium normalized the response. Alam et al. (1995) also presented evidence that cyclic adenosine monophosphate (cAMP) production can be impaired in EFA deficiency, which would manifest as decreased sensitivity to catecholamines, with subsequent reduced thermogenesis. Clandinin et al. (1992) similarly showed that linoleic acid increased the binding of insulin to adipose tissue cells (and thus improved their metabolic responses). These researchers also reported that omega-3 EFAs increased the responsiveness of muscles to insulin, and significantly increased the rate of glucose uptake by the muscle. Takada et al. (1994) showed that a dietary intake of gammalinolenic acid increased the ability of the liver to oxidize fats.

At an empirical level, Bucci (1994) cites studies which have shown that supplementation with long chain omega-3 EFAs (from fish oil) improves aerobic metabolism, while some research groups (Cunnane et al., 1986; Jones and Schoeller, 1988) have shown that increases in EFA intake improve rates of weight loss by a presumed thermogenic mechanism and also improve the efficiency of energy-generating metabolic processes in the body.

It has been pointed out that relative EFA deficiency may affect a large proportion of the population (Siguel and Lerman, 1994), therefore if Ephedra or Advantra Z® is to be used to best effect in weight loss, assuring an adequate EFA intake may be an important concomitant.

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