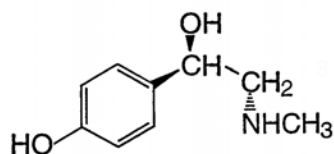


The differences between Citrus aurantium extract (Advantra Z®) and Ephedra extract:

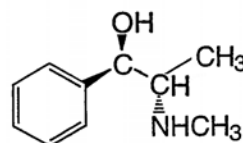
The alkaloids from Citrus species are biologically and physiologically distinct from those found in Ephedra, and possess properties that are **not** shared with the Ephedra alkaloids. The converse is also true; the Ephedra alkaloids possess properties that are not shared with the Citrus alkaloids. Scientifically, this is in part due to differences in pharmacokinetics and pharmacodynamics. The most obvious difference is that the Citrus alkaloids, unlike the Ephedra alkaloids, do not readily pass into the brain. The main factor governing the transfer of small molecules into the central nervous system is lipophilicity, and to quote from Wilkinson (2001):

“The distribution of drugs into the CNS from the blood is unique, because functional barriers are present that restrict entry of drugs into this critical site. One reason for this is that the brain capillary endothelial cells have continuous tight junctions; therefore, drug penetration into the brain depends on transcellular rather than paracellular transport between cells. The unique characteristics of pericapillary glial cells also contribute to the blood-brain barrier. At the choroid plexus, a similar blood-cerebrospinal fluid (CSF) barrier is present, except that it is epithelial cells that are joined by tight junctions rather than endothelial cells. As a result, the lipid solubility of the nonionized and unbound species of the drug is an important determinant of its uptake by the brain; the more lipophilic it is, the more likely it is to cross the blood-brain barrier. This situation often is used in drug design to alter brain distribution”

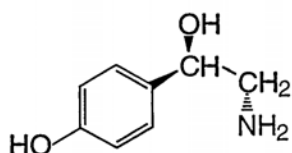
As can be seen from the comparison of the structures of synephrine and octopamine with those of ephedrine and norephedrine, synephrine and octopamine (two of the five main alkaloids present in Citrus aurantium extract) both possess aromatic hydroxy substituents, which reduce their lipophilicity substantially, particularly because of their non-hindered para-orientation, and furthermore they **lack** the β -methyl substituent of the aliphatic sidechain which is characteristic of ephedrine and its congeners, thus further reducing lipophilicity:



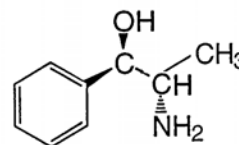
Synephrine



Ephedrine



Octopamine



Norephedrine

The same comparison can be made between other Citrus and Ephedra alkaloids, but since synephrine itself predominates in the mixture that characterizes the extract (and is also in part converted to octopamine in the body) such further comparison is redundant (a figure showing the structures of the 5 main citrus alkaloids is appended).

As a consequence of their low lipophilicity, the **Citrus** alkaloids have no effects on the central nervous system (CNS) and since the CNS actions of the **Ephedra** alkaloids are responsible for at least some of the reported Ephedra side effects, the Citrus alkaloids are entirely incapable of causing similar side effects.

In terms of effects in the periphery, while all the Citrus alkaloids are indirect-acting adrenergic agents, they are very much weaker than the Ephedra alkaloids. However, it has been shown that both synephrine and octopamine (the latter also present in the Citrus alkaloid mixture) can specifically and directly stimulate so-called β -3 receptors, the receptors believed to be mainly responsible for thermogenesis and lipolysis (the breakdown of stored fat).

The realization that there was a third type of adrenoceptor, in addition to the previously recognized β -1 and β -2 receptors, is fairly recent, having first been mooted in the late 1980's and confirmed in the early 1990's, but had been intimated by the work of Wenke et al. (1967) as long ago as the 1960's. To quote verbatim from Wenke's paper:

"By evaluating the dose-response relations in lipomobilizing sympathicomimetics, it can be shown that – in the experimental conditions used – these relations have a "simple" character in the oxedrine studied, a "quadratic" one in the used catecholamines. Only this represents the factic reality. For its explanation several attempts can be made; one of them is the model described here."

Wenke further describes a complicated mathematical model which fits his results, but the simpler explanation is that the oxedrine used (which included synephrine and octopamine) act directly on β -3 receptors, while the catecholamines used have an indirect mechanism of action. The research of Wenke also suggests strongly that synephrine is much more potent than octopamine in activating β -3 receptors.

Galitzky et al. (1993), were the first to draw attention to the qualities of octopamine as a β -3 agonist. To quote from the English summary of this paper:

"These results suggest that octopamine is a specific endogenous ligand for β 3-adrenoceptors in mammals".

However, further work by this group (Carpene et al., 1999; Fontana et al., 2000) and by an independent group in Taiwan (Yen et al., 1998) has confirmed that octopamine is indeed a specific β 3-agonist in mammalian cells. Taken together with the early observations of Wenke and his colleagues, observations made during the course of market surveillance, and the published work of Colker and his colleagues (Colker et al., 1999), it clearly indicates that synephrine and octopamine have unique properties that are **not** shown by the Ephedra alkaloids. It is obviously a property of considerable value in terms of losing weight (where the real objective is to eliminate unwanted fat) and in terms of making metabolizable substrates (fatty acids from stored fat) available as energy sources. In particular, Colker et al. showed that the weight of body fat lost in the subjects in their treatment group was greater than the actual measured loss of body weight:

Table II. Physical and metabolic changes. Unless otherwise noted, values are given as mean \pm SD.

Measure	Baseline	Week 6	Percent Change	P*
Body weight (kg)				
Group A	90.9 \pm 17.5	89.5 \pm 16	-1.5	0.05
Group B	83.6 \pm 17.5	82.7 \pm 18	-1.1	0.10
Group C	78.1 \pm 11.5	77.7 \pm 10.5	-0.05	NS
Percent body fat				
Group A	26.3 \pm 7.1	23.4 \pm 6.9	-2.9†	0.01
Group B	25.4 \pm 5.6	26.2 \pm 4.8	+1.8	NS
Group C	23.2 \pm 4.6	21.0 \pm 3.7	-2.2	0.10
Fat mass (kg)				
Group A	24.6 \pm 11.3	21.5 \pm 10.1	-13.0†	0.01
Group B	46.1 \pm 6.05	21.5 \pm 5.9	+0.3	NS
Group C	17.8 \pm 2.6	16.0 \pm 1.4	-10.0	0.10
Basal metabolic rate (kcal/d)				
Group A	2026 \pm 279	2069 \pm 268	+3.0†	0.05
Group B	1908 \pm 456	1868 \pm 437	-3.0	0.05
Group C	1859 \pm 304	1870 \pm 300	+0.1	0.10

Group A (n = 9) = treatment (*Citrus aurantium* extract, caffeine, and St. John's Wort); group B (n = 7) = maltodextrin placebo; group C (n = 4) = control.

* Paired *t* tests were used for changes over time. Repeated measures of analysis of variance were used to test time/group interactions to compare change over time among groups.

† *P* < 0.05 versus groups B and C.

In fact, the treatment group lost on average 3.1 kg of body fat, but only 1.4 kg of body weight. Since a gentle exercise programme was part of the protocol for all groups, the only logical conclusion is that the subjects in the treatment group were gaining lean body mass as they lost fat mass. Such a conclusion is entirely consistent with the anticipated action of the mixture of alkaloids in *Citrus aurantium* extract; the specific fat-mobilizing actions of synephrine and octopamine against the general background of increase in the Resting Metabolic Rate caused by the indirect adrenergic effects of all the alkaloids.

枳實 The Chinese herb Zhi shi, which is the immature Bitter Orange (*Citrus aurantium*), is used to manufacture Citrus aurantium extract. This herb, Zhi shi, has been used in Chinese medicine for several centuries for a variety of purposes, including as a digestive aid, generally in doses of 3 - 15 grams as a decoction, but sometimes in doses as high as 45 grams.

The herb contains about 0.8% of mixed alkaloids, with synephrine predominating (the natural form of the alkaloid is l-synephrine), so the normal dose of 3 - 15 grams would provide 24 - 120 mg of Citrus alkaloids per dose, with an intake of as much as 360 mg not being unusual. There are no reports of side effects at these dosage levels. In addition to administering the herb itself as a decoction, extracts are also administered by the intravenous route in the treatment of shock, in doses equivalent to 10 - 40 grams (80 - 320 mg alkaloids). The following instructions come from Ou Ming (1989):

用法 煎劑：一般 3 ~ 15 克，治內臟下垂 15 ~ 45 克。

製劑：枳實注射液：用於休克，首先以 10 ~ 40 克靜脈注射，繼以 20 ~ 100 克作靜脈滴注。

Administration Decoction: 3-15g; 15-45g for visceroptosis.

Injection: For shock, 10-40g IV, followed by 20-100g IV in drips.

Similar instructions for use are found in other Chinese reference works.

Synthetic dl-synephrine is used therapeutically world-wide, often under the name oxedrine. The recommended dosage is 100 - 150 mg three times daily, with a maximum daily intake of 600 mg. At these dose levels the only reported side effects are rarely bradycardia (**slowing** of the heart rate; ephedrine, the main constituent of the Ephedra alkaloids, **increases** the heart rate) and exacerbation of narrow-angle glaucoma. Attached PDF files cover use of European specialties containing "oxedrine", obtained from BIAM and the Compendium Suisse des Medicaments; an excerpt from the latter gives information on Sympalept® drops (Streuli, Switzerland):

Composition: *Principe actif:* tartrate d'oxédrine 100 mg.

Posologie/Mode d'emploi: *Adultes* 20 à 30 gouttes (100 à 150 mg) 3 fois par jour.

Prendre Sympalept environ ½ heure avant les repas à jeun. Administrer de préférence les gouttes non diluées sur un morceau de sucre.

Limitations d'emploi

Contre-indications: Allergie à l'oxédrine, thyrotoxicose, glaucome, troubles graves du rythme cardiaque, phéochromocytome, adénome de la prostate avec résidu urinaire et hypertension artérielle. Lors de la décompensation d'une insuffisance cardiaque ou d'une insuffisance coronarienne sévère, la seule prise d'oxédrine peut entraîner une aggravation de la situation cardiaque, y compris parfois un infarctus du myocarde.

Mesures de précaution: Une prudence particulière est de mise chez les patients qui présentent une artériosclérose, une insuffisance coronarienne, un infarctus récent du myocarde ou d'autres affections cardiaques et vasculaires organiques. Il convient en outre d'être prudent dans les tachycardies et/ou les troubles du rythme et chez les diabétiques. Débuter Sympalept à une posologie aussi faible que possible dans les affections rénales et hépatiques sévères. Après un arrêt brusque du traitement, il faut s'attendre à la possibilité d'une bradycardie et d'une chute tensionnelle. L'administration de doses élevées peut perturber la capacité de conduire un véhicule ou de manier des machines, du fait des modifications circulatoires et de l'action sur la capacité de réaction.

Effets indésirables: Une sensibilité particulière du patient et/ou une posologie élevée peuvent entraîner une agitation, une angoisse, une insomnie, des céphalées, un tremblement, des vertiges, une horripilation, des frissons et des palpitations, rarement également des accès sudoraux, des nausées et des vomissements. Il convient dans ces cas de réduire la posologie, d'interrompre ou d'arrêter le traitement.

Interactions: De nombreux médicaments, administrés de façon concomitante, peuvent agir sur les effets de l'oxédrine. On peut observer par exemple une majoration des effets après administration d'antidépresseurs tricycliques, d'inhibiteurs de la MAO, d'halotane et de cyclopropane, de médicaments à effets atropiniques, de théophylline et de ses dérivés, d'éthanol, de lévodopa ou d'ocytocine. Une atténuation des effets peut se voir par exemple après administration de phénothiazines, de b-bloquants (risque d'une bradycardie réflexe), de substances entraînant une alcalinisation des urines ou d'anti-hypertenseurs.

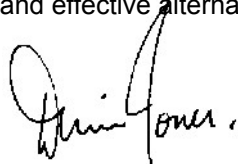
Surdosage: Un surdosage aigu accentue les effets indésirables mentionnés ci-dessus et peut occasionner en outre une élévation de la pression artérielle, une tachycardie, des extra-systoles ventriculaires et des crises d'angor. Ces symptômes régressent en règle spontanément et rapidement en raison de la demi-vie relativement brève du principe actif après l'arrêt du produit.

In comparison to the above, the single and daily intakes of alkaloids from most products based on Citrus aurantium extract are from 12 - 60 mg as a single dose, with 36 - 180 mg total daily intake!

To date, there have been at least five clinical studies performed with products containing Citrus aurantium extract in these dose ranges (Opus cit.; Kaats et al., 2002; Larocque et al., 2003; unpublished studies sponsored by Enforma, Herbalife and Nutratech), as well as several metabolic studies in human volunteers (Gougeon et al., ongoing studies which are in the process of being prepared for publication). There were no side effects observed in any of these studies. In particular, there were no effects seen on heart rate or blood pressure. Market surveillance covering many thousands of "user-days" has also failed to reveal adverse effects, thus indicating that Citrus aurantium extract is indeed a safe and effective alternative to Ephedra.

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