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Flavonoids—the forgotten factor

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Before 1990 the impact of plant flavonoids on mammalian biology was principally centered on immunity, inflammation, lipid peroxidation, oxyradicals quenching and cancer. Scanty indications existed in the literature of their effects on the central nervous system (Harborne, 1994).

Chrysin (5,7-dihydroxyflavone, isolated from *Passiflora coerulea*, (a plant used traditionally as sedative), was the first monoflavonoid described as a specific ligand for the brain benzodiazepine receptors (BDZ-R), which was active in mice inducing an anxiolytic-like effect in them. Chrysin is almost equipotent to diazepam as an anxiolytic drug, with the advantage that it does not cause sedative, analgesic or amnesic effects. The same properties were found in apigenin (5,7,4`-trihidroxyflavone), isolated from *Matricaria recutita*, another plant used as a sedative in popular medicine and in flavone which is the benzopyrone skeleton common to both chrysin and apigenin and is also found free in plants (Harborne 1994, p.285). Quite recently, other naturally occurring flavonoids have been shown to posses very mild anxiolytic properties or to exhibit low affinity for the BDZ-Rs. Among them the flavonoid cirsiliol (5,3`,4`-trihidroxy, 6,7-dimethoxy flavone), isolated from the sedative hypnotic plant *Salvia guaranitica* has pharmacological properties that may explain those of the plant extracts (see Medina et al., 1997, for review). Since cirsiliol is ten fold more potent in displacing zolpidem binding than flunitrazepam binding to BDZ_1Rs it is tempting to suggest that cirsiliol causes depressant effects by interacting with BDZ-Rs type I.

Semisynthetic derivatives of flavone, or 6-methylflavone, obtained introducing halogens, nitro groups, or both, in their molecules were found to be high affinity ligands for the BDZ-Rs. Among them we may mention 6-bromoflavone, Ki= 70 nM; 6,3'-dinitroflavone, Ki= 26 nM; 6-nitro-3`-bromoflavone, Ki= 25 nM; 6-methyl-3`-bromoflavone, Ki= 23 nM; 6,3`-dibromoflavone, Ki= 19nM; 6-chloro-3`-nitro flavone, Ki= 8nM; and 6-bromo-3'-nitroflavone, Ki= 1.5nM. These derivatives are active *in vivo* and although one of them *viz.* 6-bromoflavone, is a full agonist, (Table 1), others like 6,3'-dinitroflavone and 6-bromo-3'-nitroflavone are partial agonists while preserving the same pharmacological profile of chrysin and apigenin. Still others are antagonists (Table 1). 6,3'-Dinitroflavone is an anxiolytic drug 30 times more potent that diazepam and together with 6-bromo-3'-nitroflavone both exhibit a wide separation between anxiolytic and sedative doses which indicates a greater pharmacological selectivity than for instance, the benzodiazepine diazepam.

Table 1: Pharmacological profile of selected natural or synthetic flavonoids with high affinity for the BDZ-Rs.

Flavonoid	**Profile**
Flavone	partial agonist
Chrysin	partial agonist
Apigenin	partial agonist
Cirsiliol	agonist
6-bromoflavone	full agonist
6,3'-dinitroflavone	partial agonist
6-bromo-3'-nitroflavone	partial agonist
6-chloro-3'-nitroflavone	antagonist

The evidence now existing (Medina et al., 1997), indicates that the flavonoids studied act on the central nervous system, at least through the activation of the BDZ-Rs and many of them possess the properties of "tranquilizing" drugs.

References

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