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Ginger and Acmella, together in Indena's Mitidol®: a rational combination for effective ache relief support

Globally, it has been estimated that 1 in 5 adults suffer from pain and that another 1 in 10 adults are diagnosed with chronic pain each year.(1) Pain affects all populations, regardless of age, sex, income, race/ethnicity, or geography and the four largest causes of pain are cancer, osteo- and rheumatoid arthritis, operations and injuries, and spinal problems.

Given such a scenario, research and remedies for pain management is a priority for public health. An important help may come from the nature, for instance from plants whose active ingredients could selectively act on cannabinoid CB2 receptors, such as cannabidiol, which represent an attractive target in obtaining an anti-inflammatory and analgesic effect without central nervous system side-effects.

That's why Indena has been focusing for years in developing an innovative supportive ingredient to face one of the most relevant global health problems, ache management. The result of this research commitment is Indena's Mitidol®, the proprietary combination of a couple of botanicals working together very effectively: ginger (*Zingiber officinale*) and acmella (*Acmella oleracea* L.). Mitidol®'s efficacy has been proven by in-vitro and human studies.

Ginger (*Zingiber officinale Roscoe*) rhizome is one of the hot spices belonging to *Zingiberaceae* family, a herbaceous perennial plant native to Southern Asia. The main components of ginger extracts are gingerols and shogaols.

Ginger rhizome is extensively consumed as a spice in foods and beverages because of its characteristic pungency and piquant flavor. It is also used in traditional oriental medicine (Ayurvedic, Chinese, and Unani systems of medicine) since antiquity to treat different

diseases (such as rheumatoid arthritis, sprains and muscular aches, sore throats, nausea, constipation and indigestion, fever, infectious diseases, helminthiasis) as it has antibacterial, antiviral, analgesic, and antipyretic properties.

The pungency of the fresh ginger rhizome is due to gingerols, of which the major pungent principle is [6]-gingerol (1-[40-hydroxy-30-methoxyphenyl]-5-hydroxy-3-decanone) and the most abundant constituent among the gingerols. The pungency of dried or cooked ginger is due to nonvolatile phenylpropanoid-derived compounds from gingerols, namely, shogaols. The less pungent zingerone is also produced from gingerols during drying process. Ginger also contains acrid resinous substances (5–8 %).

The major properties of ginger compounds include immune-modulatory, anti-inflammatory, anti-tumorigenic, anti-hyperglycemic, and anti-lipidemic actions. (2)

Acmella is a flowering herb species in Asteraceae o Compositae's family. Indena has been one of the first companies to study in depth the efficacy of acmella through Indena's usual scientific approach.

The plant's native distribution is unclear, but it is likely derived from Brazil, where it is called jambu and has been used for centuries to treat oral pain because of its analgesic properties. The whole plant is used as a medicinal remedy in various parts of the world. When chewed, the leaves and flowers generate a tingling sensation to the lips and tongue. This sensation is caused by the action of spilanthol, an isobutylamide compound that promotes local anesthetic action treating the tooth ache. (3)

Spilanthes (*Compositae* or *Asteraceae*) is a genus comprising of over 60 species and *Spilanthes acmella* (*syn. Acmella oleracea*), has been well documented for its uses as spices, as antiseptic, antibacterial, antifungal, and antimalarial, treatment, and as remedy for toothache, flu, cough, rabies diseases, and tuberculosis. (4) Acmella's main constituents are lipophilic alkylamides or alkamides bearing different numbers of unsaturated hydrocarbons (alkenes and alkynes), such as spilanthol, which is the main compound isolated from many parts of this plant, particularly flowers. Spilanthol has many biological activities, including analgesic, antinociceptive, antioxidant, anti-inflammatory, antiwrinkle. (3)

From the very beginning of its research on acmella, Indena have been focused on producing a high-quality extract starting from a high-quality biomass, not an easy goal considering the poor quality of acmella's biomass coming from the tropical or far east countries. Therefore, the company invested in a proprietary cultivation looking for the most suitable farmland in Italy. Since three years, in the Italian region of Sardinia the company grows its own *Spilanthes acmella* plants, which give excellent biomass in terms of purity and quality thanks to organic and sustainable farming practices. For the first time a "made in Italy" acmella has been produced and it's one of the point of strength and of peculiarity of Indena's Mitidol®.

As reported by literature data, both *Zingiber officinale* and *Acmella oleracea* extracts can be useful as inflammation and ache modulators. Indena's innovative solution is to exploit the synergy of the two standardized extracts together, which have been proven to provide a healthy inflammatory and ache relief support action. Mitidol® is the result of that effort, a rational combination of ginger and acmella.

The mechanism of action and the efficacy of Mitidol® have been reported in a study very recently published (January 2020) (5), which tested the new food-grade formulation of *Acmella oleracea* and *Zingiber officinale* in two in-vitro assays in order to verify its effect on endocannabinoid system.

The study includes a cell-based assay in human recombinant Cannabinoid 2 Receptor cells, in order to evaluate a possible agonist effect on those receptors, and a Fatty Acid Amide Hydrolase inhibition activity assay, to evaluate potential inhibition of that hydrolase, which, as said, is responsible for degradation of the endogenous cannabinoid anandamide. The results prove that the combination of the two extracts in the Mitidol® formulation has a double effect on ache relief support: a direct one thanks to the interaction with CB2 receptors and an indirect effect through the inhibition of FAAH enzyme.

Another important one-month human study has been very recently completed in the area of joint health, to show Mitidol®'s efficacy in supporting knee functionality and comfort. (6)

The human study involved 50 subjects with knee challenges who have got a 30-day supplementation with Mitidol®. As for main results, individuals report a remarkable support in the relief from ache starting from 7 days; the optimization of knee function, confirmed with 2 different tests (Lhysolm scale and WOMAC scale); an improvement of the quality of life (SF-36 questionnaire) and of the physical wellbeing. This last health progress resulted in a consequent reduction of BMI – Body Mass Index, since the less pain people feel, the more they move. At the same time, objectively measurable parameters show that Mitidol® maintains a healthy inflammatory response after 1 month supplementation: -12,7 % ESR - Erythrocyte Sedimentation Rate, and -36,4 % CRP – high sensitivity C-Reactive Protein.

Mitidol®, the combination of *Zingiber officinale* and *Acmella oleracea*, may therefore be considered as a natural adjuvant in supporting ache relief. Moreover, it's available for easy development and manufacture of solid oral dosage forms (e.g. capsules, tablets), thanks to its innovative smart formulation which combines the two oily liquid extracts in a unique fine-powder ingredient.

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