mitidol®

The amazing couple
for an actual relief from ache.

indena®
SCIENCE IS OUR NATURE

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1.

Facing a global health problem, with the help of nature

As highlighted by the most authoritative official sources, such as WHO or IASP (International Association for the Study of Pain), pain is an enormous global health problem.

[1] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3201926/#B1

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.

[2] https://www.packagedfacts.com/Pain-Management-Consumer-10595686/

Despite advances in medicine and numerous agents that counteract pain, millions of people continue to suffer. **That's why research and remedies for pain management is a priority for public health.**

Recent analysis revealed 5 top trends in pain management for 2017[2]:

Growth in alternative therapies: as of 2016, roughly **23% of adults trust homeopathic medicine**, and 22% prefer alternative medicine to standard medical practices;

Heavier focus on **health and diet**: health and diet tools — ranging from functional foods and beverages to organic and natural and beyond — have a significant role to play in satiating that hunger and achieving the universal goal of a more fulfilled life;

Exercise and weight management as a part of broader treatment;

Rising interest in **homeopathic and functional pain medication**: makers and marketers should consider adding **homeopathic or herbal qualities** that can help users feel like they are doing something healthy for their entire body and not just eradicating their pain;

Caffeine for more than just coffee.

An **important help** may come from 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.

Indena has been focused for years in developing an innovative product which could give an actual relief from ache:
Mitidol®

Today it's available, thanks to a couple of botanicals working together in a very effective way:
ginger (*Zingiber officinale*)
and **acmella (*Acmella oleracea* L.).**

2.

Ginger, the power of nature to modulate healthy inflammatory response

Ginger (*Zingiber officinale* Roscoe) rhizome is **one of the hot spices belonging to *Zingiberaceae* family**, a herbaceous perennial plant native to Southern Asia.

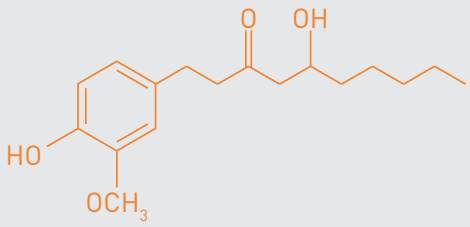
> **Ginger rhizome is extensively consumed as a spice in foods and beverages because of its characteristic pungency and piquant flavor. It is used in a variety of foods and also in carbonated drinks, in liquors and as a preserve in sugar syrup (murabba).**

Ginger is an **excellent source of several bioactive phenolics**, including non-volatile pungent compounds such as gingerols, paradols, shogaols, and zingerones.

It is also **used in traditional oriental medicine** (Ayurvedic, Chinese, and Unani systems of medicine) since antiquity to treat different diseases that include rheumatoid arthritis, sprains and muscular aches, sore throat, nausea, constipation and indigestion, fever, infectious diseases, and helminthiasis.

Ginger is particularly valued in medicine as a carminative and stimulant to the gastrointestinal tract and it's known to increase the motility of the gastrointestinal tract and has antibacterial, antiviral, analgesic, and antipyretic properties.

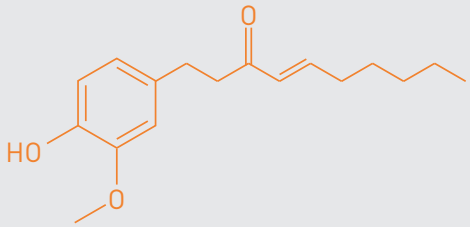
The pungency of the fresh ginger rhizome is due to gingerols, of which the major pungent principle is [6]-gingerol (1-[40-hydroxy-30-methoxyphenyl]-5-hydroxy-3-decanone), an oily liquid, and the most abundant constituent among the gingerols.



6-Gingerol

(Pungent compound in fresh ginger)

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%).



Shogaol

(Pungent constituent of ginger produced on drying or cooking)

Gingerols and shogaols are the main components of ginger extracts.

The major properties of ginger compounds include **immune modulatory, anti-inflammatory, anti-tumorigenic, anti-hyperglycemic, and anti-lipidemic actions.**[3]

[3] Krishnapura Srinivasan, Ginger rhizomes (*Zingiber officinale*): A spice with multiple health beneficial potentials, PharmaNutrition 5 (2017) 18–28

3.

Acmella: from Sardinia a “made in Italy” biomass, powered by Indena

Acmella is a flowering herb species in Asteraceae o Compositae's family. It is grown as an ornamental or medicinal plant and attracts fireflies when in bloom. A small, erect plant, it grows quickly and bears gold or red inflorescences. It is frost-sensitive but perennial in warmer climates.

The whole plant is used as a medicinal remedy in various parts of the world.

Acmella has been used for centuries to treat oral pain because of its analgesic properties. The leaves and inflorescence are used as household medicine to treat oral and throat diseases.

Acmella flower is then also known as the **"tootache plant"**. 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 toothache.[4]

60

Spilanthes (Compositae or Asteraceae) is a genus comprising of over **60 species**.

***Spilanthes (Compositae* or *Asteraceae)* is a genus comprising of over 60 species and *Spilanthes acmella*, has been well documented for its uses as spice, antiseptic, antibacterial, antifungal, antimalarial treatment, and as remedy for toothache, flu, cough, rabies diseases, and tuberculosis.**[5]

Despite being a remedy used for centuries in the territories of origin, acmella has not been widely exploited in nutraceuticals so far.

Indena has been one of the first company to study in depth the efficacy of that plant through Indena's usual scientific approach. Mitidol® is the result of this research commitment that goes back many years.

[4] Mariangela Rondanelli, Federica Fossari, Viviana Vecchio, Valentina Braschi, Antonella Riva, Pietro Allegrini, Giovanna Petrangolini, Giancarlo Iannello, Milena Anna Faliva, Gabriella Peroni, Mara Nichetti, Clara Gasparri, Daniele Spadaccini, Vittoria Infantino, Sakina Mustafa, Tariq Alalwan, Simone Perna, *Acmella oleracea* for pain management, Fitoterapia 140 (2020) 104419

[5] Suchita Dubey, Siddhartha Maity, Mahendra Singh, Shubhini A. Saraf, and Sudipta Saha, Phytochemistry, Pharmacology and Toxicology of *Spilanthes acmella*: A Review, Advances in Pharmacological Sciences Volume 2013, Article ID 423750, 9 pages

As quality of raw material is one of the most important prerequisite for a quality extract, Indena had to find a good acmella's biomass for Mitidol® production. Considering the poor quality of biomass coming from the tropical or far east countries, **the company decided to invest 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.**

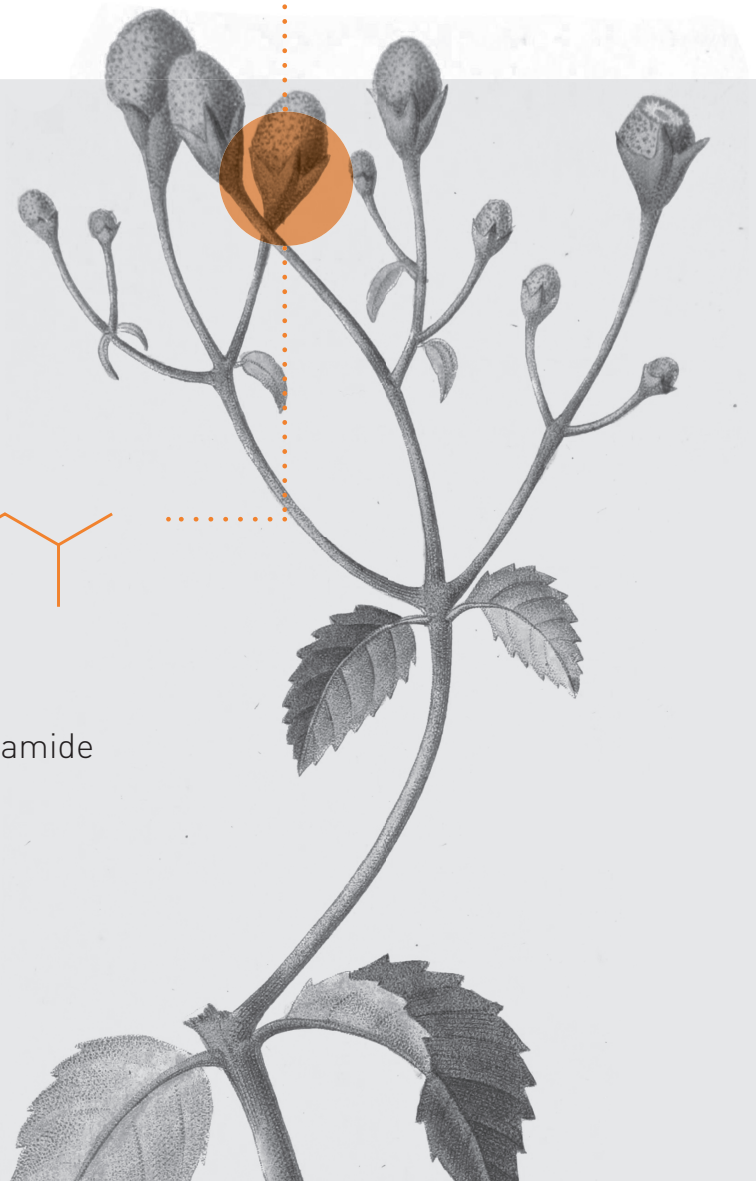
For the first time a “made in Italy” acmella has been produced and it’s one of the point of strength and of peculiarity of Indena’s Mitidol®.

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**.[6]

[6] M. Rondanelli, et al., *Acmella oleracea* for pain management, Fitoterapia 140 (2020) 104419 – già citata sopra.

Spilanthol
(2E, 6Z, 8E)-N-isobutyldeca-2,6,8-trienamide



4.

The amazing couple: acmella and ginger working together for ache management

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 amazing couple, through the rational combination of the two standardized extracts, which have been proven to provide a healthy inflammatory and ache relief support action.

Starting from such an idea and considering Indena's pioneering commitment to acmella and the availability of quality raw materials from its crops in Sardinia, the company has made technological efforts to associate the two botanical extracts together, with the purpose of create a unique and very effective product.

> **The result of that effort is Mitidol®, the combination of ginger and acmella with an innovative formulation which blends the two oily liquid extracts in a unique fine-powder ingredient.**

Mitidol®'s mechanism of action and efficacy have been reported in a study very recently published (January 2020).[7]

In the study, the new food-grade formulation of *Acmella oleracea* and *Zingiber officinale* was tested in two in-vitro assays in order to verify its effect on endocannabinoid system.

Endocannabinoid system includes CB1 receptors, found primarily in the brain and in central nervous system, and CB2 receptors which are mostly in the peripheral organs, especially in cells associated to the immune system.

Endocannabinoid system is linked to many human organism functions, among which are immune or cardiovascular ones, neuroprotection, fertility, memory and pain modulation.
FAAH (= Fatty Acid Amide Hydrolase) is an enzyme which breaks down anandamide (AEA=N-Arachidonoylethanolamine), an endogenous cannabinoid, able to activate both CB1 (brain and CNS) and CB2 (periferical organs) receptors: **FAAH inhibition leads then to long-lasting effect of AEA.**

The mentioned study on Mitidol® 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.

From the evidence that emerged in the experiments made in the study, **the combination of the two extracts in the Mitidol® formulation has a proven double effect on ache relief** support: a direct one thanks to the interaction with **CB2 receptors**, the same target on which the CBD – cannabidiol acts; and an indirect effect through the inhibition of **FAAH enzyme**.

Conditions affecting joint health are very common nowadays, for example osteoarthritis is ranked as the 11th highest contributor to global disability in the world and is predicted to become the fourth leading cause of disability worldwide by 2020.[8]

[7] Giovanna Petrangolini, Fabio Donzelli, Davide Berlanda, Pietro Allegrini, Andrea Rossignoli, Michela Stucchi, Antonella Riva, Targeting Cannabinoid Receptors and Fatty Acid Amide Hydrolase: An Innovative Food-Grade Delivery System of *Zingiber officinale* and *Acmella oleracea* Extracts as Natural Adjuvant in Pain Management, J Nutr Food Sci, Vol. 9 Iss. 5 No: 766

[8] Cross M, Smith E, Hoy D, et al. The global burden of hip and knee osteoarthritis: estimates from the Global Burden of Disease 2010 study. Ann Rheum Dis. 2014;73(7):1323-1330. doi:10.1136/annrheumdis-2013-204763

Care and management of knee OA pain remains very complex. Despite advances in medicine and numerous agents that counteract knee OA pain, **millions of people continue to suffer from it.**

Recently, attention has been given in the identification of novel botanicals interventions supporting pain relief, like ginger and acmella do. Therefore, they're dietary botanicals supplements potentially useful in supporting ache relief also in case of OA. **In this area, an important one-month human study has been very recently completed to show Mitidol®'s efficacy in supporting knee functionality and comfort.**[9]

The human study involved 50 subjects with knee challenges who've got a 30-day supplementation with Mitidol®.

The main results include both individual and objective evidences. Individuals report: a **remarkable support in the relief from ache starting from 7 days**; **optimization of knee function, confirmed with 2 different tests** (Lhysolm scale and WOMAC scale); **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 more comfort people feel, the more they move. At the same time, objectively parameters show that **Mitidol® maintains a healthy inflammatory response after 1 month of supplementation:** - 12,7 % ESR - Erythrocyte Sedimentation Rate, and -36,4% CRP - high sensitivity C-Reactive Protein.

In conclusion, these results suggest a strong rationale for the use of Mitidol®, the combination of *Zingiber officinale* and *Acmella oleracea*, as a natural adjuvant in supporting ache relief.
Moreover, Mitidol® is also a smart formulation which combines 2 oily extracts in a powder ingredient, suitable for easy development and manufacture of solid oral dosage forms (e.g. capsules, tablets).

[9] Mariangela Rondanelli, Antonella Riva, Pietro Allegrini, Milena Anna Faliva, Maurizio Naso, Gabriella Peroni, Mara Nichetti, Clara Gasparri, Daniele Spadaccini, Giancarlo Iannello, Infantino Vittoria, Teresa Fazia, Luisa Bernardinelli, Simone Perna, Manuscript accepted for publication

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