ADVISORY BOARD

quality in food supplements of botanical origin

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FOOD SUPPLEMENTS OF BOTANICAL ORIGIN: A MULTIDISCIPLINARY APPROACH TO QUALITY. The case of turmeric.

Milan,
29th January 2020

[Consensus Paper

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ABSTRACT

The botanical supplements sector comprises a huge range of products which vary significantly from one to another, not least for different degrees of attention and transparency given to quality and safety. This is why for doctors, pharmacists and consumers alike, quality should be a defining criterion in the choice of supplement and an essential requirement for information and transparency.

The need for clarification underlies the establishment of the **Advisory Board on Quality in Food Supplements of Botanic Origin**, a multidisciplinary panel of Italian and international experts dedicated precisely to this topic.

Deliberations on the part of the experts on this Board have led to the draft of the first Consensus Paper: **Food Supplements of Botanical Origin: a Multidisciplinary Approach to Quality**, a document that addresses the issues of quality, efficacy and safety of botanicals based on scientific evidence and clinical experience.

Turmeric is the the special focus of the Consensus Paper, which offers scientific evidence about the quality, efficacy and safety of one of the most studied and widely consumed botanical extracts in the world.

INTRODUCTION

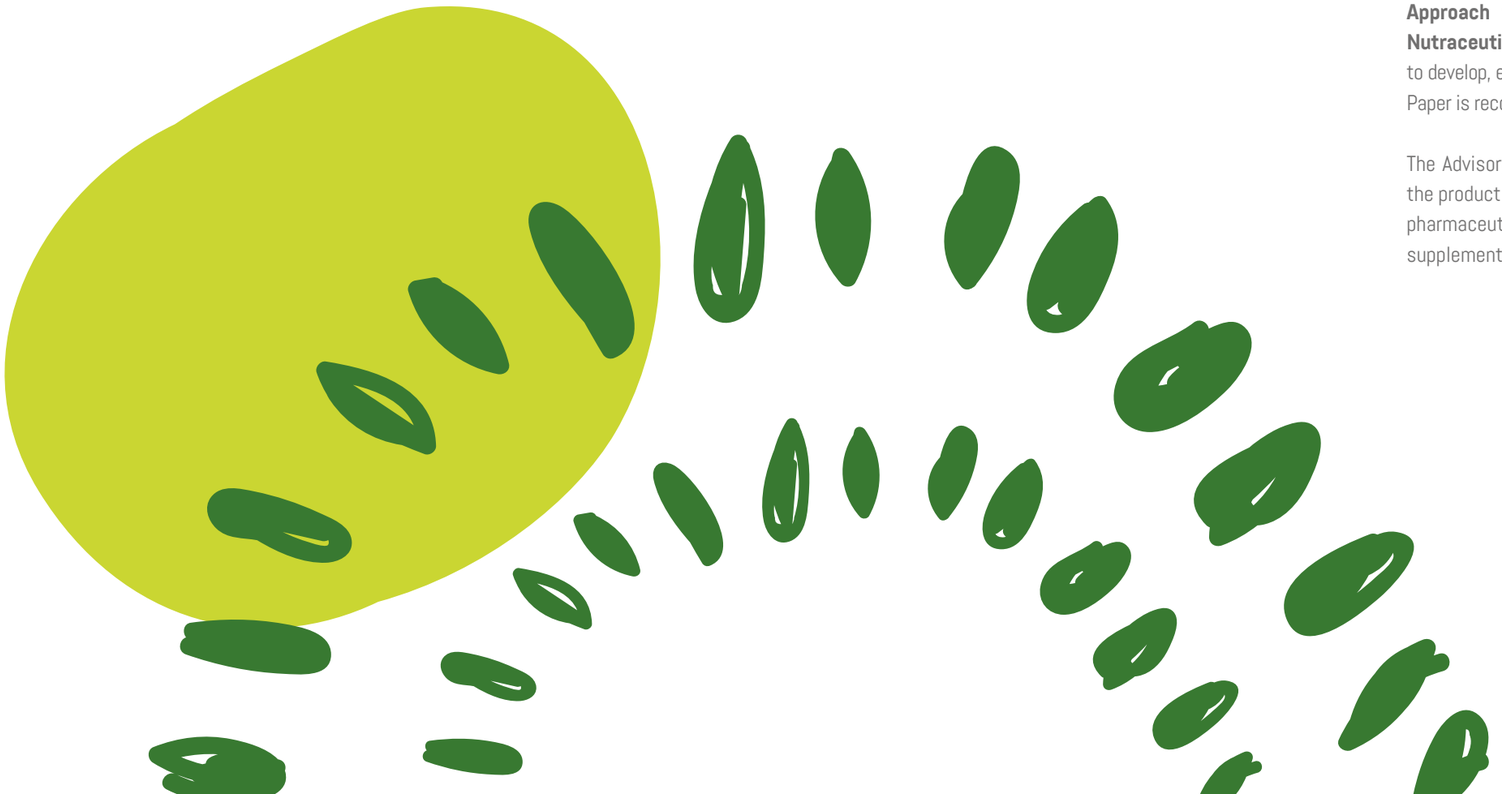
According to a report on the social value of the food supplement, published by the Italian social Studies Institute Censis in 2019[1], 32 million Italians take food supplements, of which 18.7 million are regular users. Product consumption cuts across gender, age, schooling, location and economic condition, and can be attributed to recognition of their contribution to healthcare.

The Censis Report also highlights two important challenges for the food supplement sector:

- *to provide safe, high quality products, which match the growing expectations of the populace by drawing on the best knowhow in the field;*
- *to create effective authenticated communication, designed to convey expert knowledge and medical opinion.*

In a sector that includes a very large quantity of very different products not least for different degrees of attention and transparency given to quality and safety, quality is decisive as a criterion of choice for doctors, pharmacists and consumers, and an essential requirement for correct transparent information.

What do we understand by quality supplements?
What elements allow us to evaluate the quality, safety and efficacy of the products?
What are the risks of "do it yourself"?
What are the criteria for the correct use of food supplements?
How should proper information be provided?



To clarify these issues and provide common guidelines, supported by rigorous scientific evidence and clinical experience, the Quality Supplements Advisory Board has been set up; a multidisciplinary panel of Italian and international experts to deal with botanical supplements.

This Consensus Paper is the first result of the work of the Advisory Board. Its objective is to address general aspects relating to the quality of botanical supplements. There will be deeper exploration in subsequent publications of the specificities of different plant extracts used in nutraceuticals[2]. The in-depth analysis which is the main focus of this first Consensus Paper is related to the widely used ingredient turmeric; according to IQVIA data, 4.9 million packs of supplements containing turmeric were sold in Italy from July 2018 to June 2019[8].

The Consensus Paper: **Food Supplements of Botanical Origin: a Multidisciplinary Approach to Quality** has received the backing of the **Italian Society of Nutraceuticals – (SINut)** (an independent non-profit association which undertakes to develop, encourage and promote nutraceutical research). The scientific value of the Paper is recognised and deemed consistent with the objectives of the association.

The Advisory Board was created on the initiative of Indena, a leading company in the production of quality botanical ingredients and supplements, and of Scharper, a pharmaceutical company also with a history of development and marketing of food supplements promoted exclusively to the medical profession.

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OBJECTIVES AND METHODS

The Consensus Paper: **Food Supplements of Botanical Origin: a Multidisciplinary Approach to Quality** aims to make available to doctors, pharmacists, consumers, and the media, a scientifically authoritative source that clarifies the issues of quality, safety and efficacy of supplements of botanical origin, helping these interlocutors to orient themselves in the vast and varied panorama of food supplements.

The authors of this Consensus Paper, who make up the Advisory Board on quality supplements, are experts with different specializations chosen from the leading authorities on botanical extracts and in particular on turmeric, which is the focus of this document.

Careful analysis of scientific literature and the comparison of clinical practice experiences were the basis of the joint work that led the group of experts to formulate the indications and recommendations contained in this document.

WHAT ARE FOOD SUPPLEMENTS OF BOTANICAL ORIGIN?

The European Directive 2002/46 / EC of 10th June 2002, ratified in Italian Law by Legislative Decree n°169 of 21st May 2004, defines food supplements as follows: *"food products intended to supplement the common diet and which constitute a concentrated source of nutrients, such as vitamins and minerals, or of other substances having a nutritional or physiological effect, in particular, but not exclusively, amino acids, essential fatty acids, fibre and extracts of vegetable origin, whether single or multi-component, in pre-dosed forms, such as capsules, tablets, pills, chewing gums and the like, sachet powders, liquids contained in ampoules, dropper bottles and other similar forms of liquids and powders in pre-measured forms."*

In botanical supplements, the active ingredients are made up of substances and preparations from a plant base (botanicals), and related derivative preparations. The use of botanicals in food supplements is currently regulated in Italy by the Ministerial Decree of 10th August 2018, which also contains plants in the BELFRIT list, drawn up by the relevant authorities in Belgium and France[3].

QUALITY, SAFETY AND EFFECTIVENESS: A CLARIFICATION

The quality, safety and efficacy of a supplement are not concepts which may be superimposed:

- **quality** is determined by the characteristics of the raw material, the supply chain, the technologies and processes used for the processing of the ingredients, the controls on the raw material (botanical ingredients) and on the finished product;

- **safety** is primarily linked to the verification of the absence of potential contaminants typical of products of plant origin (eg pesticides, mycotoxins, toxic metals etc.), an aspect that pertains to quality, but also to the specific conditions of the organism that assumes the supplement, the dosage and the methods of intake and the possible interactions with other active ingredients, be they natural or synthetic. Therefore, it is essential to carry out preclinical toxicological studies to guarantee the use of the botanical ingredient. However, a quality supplement can have different safety profiles in different subjects and for this reason it is advisable that the intake of botanical supplements is preferably recommended and guided by the doctor or pharmacist;

- **efficacy** is understood to be the ability of a supplement, through its ingredients, to strengthen physiological processes: supplements containing the same ingredient of natural origin can have different effectiveness depending on the formulation, which for example modifies its solubility.

It is clear therefore that the quality, safety and efficacy, as described, are essential requirements for a supplement to be deemed as being of "quality".

HOW TO RECOGNISE THE QUALITY OF A BOTANICAL FOOD SUPPLEMENT

The quality of botanical supplements is expressed by specific characteristics, which those who prescribe or recommend the products (doctors and pharmacists) and consumers must be able to verify:

1. **quality of the raw material:**

   I. identification of the plant (at least its genus and species): the plant from which the ingredient derives must be identified with certainty, through specific protocol and analyses, such as botanical checks, chromatographic profiles, or DNA analysis;

   II. purification of the botanical extract: if the plant contains notoriously toxic or allergenic substances such as ginkgolic acids in the leaves of Ginkgo biloba, or unwanted substances such as simple sugars, it is important to remove these components and obtain an extract deemed purified;

   III. standardization is a process of combining different lots to ensure that the botanical extract always has the same composition of constituents in order to reduce the natural variability present at the outset in the plant material as well as the same titration (i.e. the concentration of the characteristic chemical class);

2. **control of the supply chain:**

I. suppliers should be accredited on the basis of rigorous criteria of quality, sustainability and traceability;

II. GAPC guidelines for good agricultural and harvesting practices should be implemented in the supply chain;

III. the need for high quality raw materials should be reconciled with the principles of biodiversity and sustainability indicated by international conventions and standards such as the Convention on Biological Diversity (CBD);

IV. the entire supply chain should be under continuous control from cultivation which is constantly monitored by agronomists and botanists, up to the delivery of the raw material to the production sites;

3. **quality of the manufacturing processes:**

I. technologically advanced and safe production plants for both raw materials and operators;

II. processes compliant with production standards and regulations such as Good Manufacturing Practices (GMP) and the Hazard Analysis Critical Control Points manual (HACCP);

III. use of high-quality, precisely defined excipients to optimize the effectiveness of the active ingredient;

IV. meticulous inspection of the finished product.

Ready access to information on the characteristics outlined above would allow assessment of the actual quality of the products and to make an informed choice on botanical supplements. The authors of this Consensus Paper therefore hope that the market will increasingly go in the direction of real transparency, and aim to serve prescribers and consumers alike.

HOW TO RECOGNISE THE QUALITY OF A BOTANICAL FOOD SUPPLEMENT

Current legislation on botanical supplements does not require evidence of efficacy based on scientific studies.
Despite this, there are products of botanical origin whose effectiveness is demonstrated by rigorous preclinical and clinical studies and conducted with methods similar to those required for drugs[4].
The effectiveness of a supplement of botanical origin with respect to the physiological function it claims to have is therefore verifiable through:

1. **availability and reliability of specific preclinical and clinical studies on the ingredient**

I. the number and reproducibility of studies;

II. reliability of the research institutes that conducted them and of the journals that published them (peer-reviewed international journals);

III. the specific nature of the studies: it is essential that the studies are devoted to a specific ingredient contained in the supplement, with its characteristics of origin, extraction, formulation, concentration, and that efficacy is not affirmed by general reference to existing literature;

2. **pharmacokinetic results** from studies dedicated to the specific product with its specific formulation (these studies verify the absorption, distribution, metabolism and elimination from the body of the ingredients believed to be active supplements): in fact, albeit with physiological equivalence, products with different formulations may have a different degree of bioavailability, a different metabolism and therefore vary in efficacy.

3. **evidence of clinical studies on healthy physiological activities**, or data that lead to evidence of the impact on physiological functions performed by the ingredient and / or by the supplement.

In order to adopt a new claim, or to be able to declare the nutritional and health claims of the product being marketed, the studies must then be validated by the technical scientific commission of the European Food Safety Authority (EFSA), in accordance with Regulation 1924/2006.

INTERACTION: A FUNDAMENTAL ASPECT OF SAFETY

The widespread trend among consumers to consider food supplements “naturally good”, together with the accessibility of these products through distribution channels where prescriptions are not required, have fostered a “do-it-yourself” habit.
This practice is to be discouraged strongly. The use of supplements of botanical origin requires an overall assessment of the condition of the person concerned, with a technical competence that can only be provided by a doctor or pharmacist.
The reasons for this warning are not dissimilar from those concerning the products of the official pharmacopoeia, namely:

1. botanically derived ingredients have physiological effects which must be known and assessed with respect to the specific situation of the individual for whom they are intended;
2. It is essential that a competent professional should assess and monitor any possible interaction between the ingredient of botanical origin that the individual is about to take and any other active ingredient being taken simultaneously, whether natural or synthetic. The absence or superficiality of an assessment of possible interaction between active ingredients, in the erroneous belief that “it is natural, therefore it can do no harm”, is actually a source of potential risk;
3. each organism responds in its own way to the ingredients of a supplement: it is therefore necessary to first analyse the general conditions of the individual in an expert manner and then evaluate the opportunity to prescribe a specific supplement and the methods of use, which include the dosage and length of treatment. For this reason, it is also necessary that the ingredients are the subject of human studies, from which their safety and tolerability can be verified.

It is therefore necessary to reiterate that botanical supplements should preferably be recommended by the doctor or pharmacist. These professionals must regard the prescription or recommendation of these products with the same rigorous approach they apply to all prescriptions, taking into account the general conditions of the individual subject and any therapies or treatments already in progress to order to assess any possible interaction and establish the most effective dosage.

FOCUS ON THE CASE OF TURMERIC

THE PLANT AND ITS ACTIVE COMPONENTS[5]

Curcuma longa L. (a member of the ginger family, Zingiberaceae) is a perennial herb plant widespread in South East Asia and extensively cultivated in China, India, Indonesia and Thailand[6].

The golden-orange rhizome from which an intense yellow ingredient is obtained is used for food and for the production of supplements. Turmeric root has been known since ancient times for its beneficial properties and is one of the most widely studied botanical products.
The turmeric plant, and in particular its rhizome, first appeared in India as a spice, as a food and for use in Ayurvedic medicine before 600 BC. Turmeric is part of the ginger family and, like ginger, grows easily in tropical climates. It probably reached China in 700 AD, West Africa from 800 AD. and the Americas around 1700 AD.

Turmeric has many different names in different countries, but is known in many languages simply as “yellow root”. This iconic colour derives from three chemically distinct compounds, which are the active components of the plant: curcumin, monodemetoxicurcumin and bisdemethoxyurcumin.
All three of these curcuminoids are often collectively referred to as curcumin, both on the market and also in scientific literature. However, it is important to remember that each curcuminoid has its specific chemical structure and its specific functional profile. Depending on its provenance and growth conditions, the rhizome contains from 2% to 9% of curcuminoids and a volatile oil composed mainly of sesquiterpenes such as zingiberene, curcumol and α and β turmerone.

The three forms of curcumin have different chemical personalities and colours and, working together or individually, have been shown to produce important physiological antioxidant, anti-inflammatory, anti-mutagenic, anti-infectious, anti-cancer effects.

As of 2019, about 100 human studies have been carried out on curcumin, involving thousands of subjects.

FUNCTIONING AT CELL LEVEL[5]

The mechanism of action of curcumin is polyvalent in that it "turns off" pro-inflammatory transcription factors such as NF-κB, AP-1, STAT, thus regulating the expression of genes involved in cell survival, cell proliferation and angiogenesis. Curcumin is also able to inhibit various kinase proteins and modulates the inflammatory response by "turning off" the inflammation enzymes such as COX-2, lipoxygenase and NO synthase. Curcumin also inhibits the production of inflammatory cytokines such as TNFα, IL -1-2-6-8- and -12. In addition, curcumin is a powerful anti-oxidant that acts as a radical scavenger by inducing antioxidant cellular defences through the activation of the nuclear factor NrF2.

PHYSIOLOGICAL AND SIDE EFFECTS[6]

In humans, the main action of curcumin is anti-inflammatory; as such, it has a beneficial effect on gastrointestinal, cardiovascular, osteoarticular and hepatic health.

Chronic inflammation is the cause of many ailments, especially of people in old age. However, chronic inflammation may also in fact be defined today as the silent killer of human health. According to the World Health Organization, over a third of the 57 million deaths worldwide each year are caused by chronic diseases (cardiovascular disease, type 2 diabetes, hypertension, respiratory disease and Alzheimer's disease) and 90% of these diseases have an inflammatory origin. Chronic inflammation is mainly the result of a typical western lifestyle: understanding its mechanisms and coping with inflammation has become a crucial goal of modern clinical research and has in fact recently been defined a priority by the National Institutes of Health in the US.

In addition to its anti-inflammatory action, curcumin has proven antioxidant, hepatoprotective, neuroprotective, antihypertensive, antiobesity, antimicrobial and antidiabetic action.
In any case, it should be remembered that the antioxidant effects and joint functions of turmeric are recognised by the Ministerial Guidelines.

The permissible daily dose of curcumin is 0 - 3 mg / kg body weight, according to the Joint Committee of Experts for Food Supplements of the United Nations and the World Health Organization (JECFA) and the European Safety Authority Food (EFSA).
The only side effects described, mainly resulting from excessive dosage, are reports of diarrhoea, nausea, dyspepsia, headache and skin rash[8].

QUALITY

The quality of turmeric, like all botanical extracts, depends primarily on the quality of the raw material and the purity of the extract.
The procedure that enables the plant to be unquestionably identified is by DNA analysis or barcoding of the plant itself.

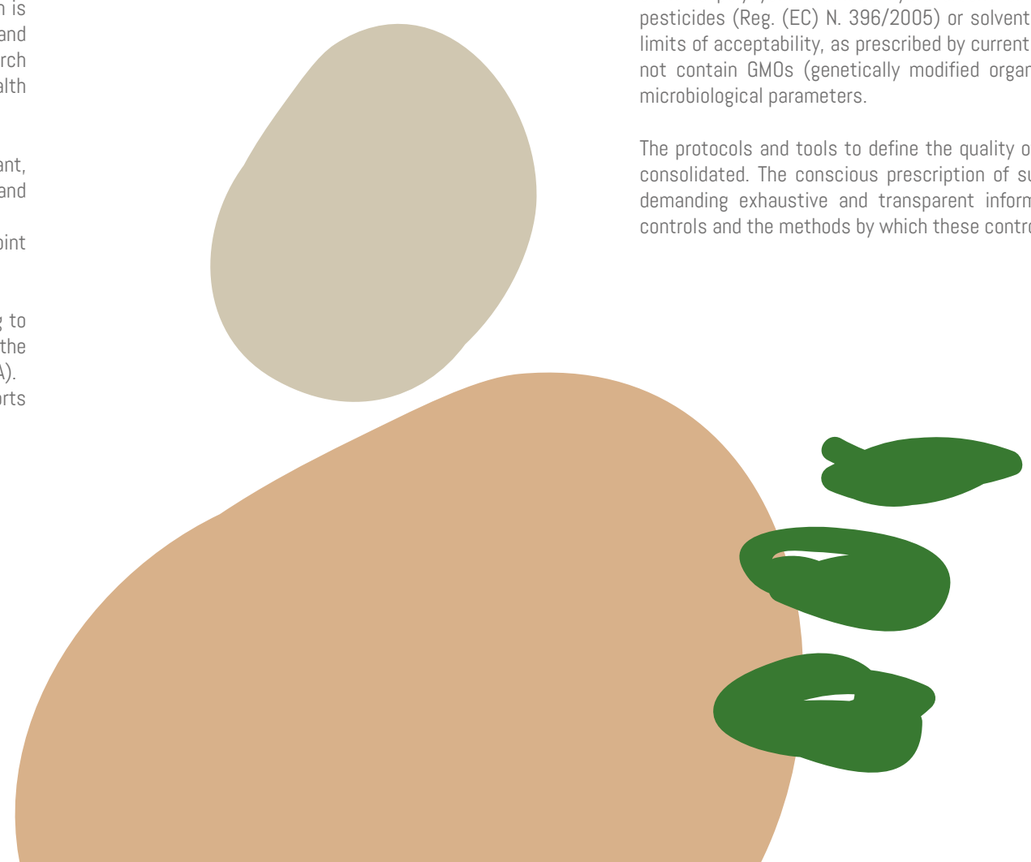
Furthermore, quality turmeric is free from contamination whether accidental or deliberate, in particular with[9]:

- species other than Curcuma longa, such as Curcuma zeodaria, Curcuma aromatica and Curcuma xanthozzhiza;
- azo dyes such as Metanil Yellow and Sudan I and IV, organic compounds not allowed as additives and prohibited for food use but used as turmeric adulterants because the absorption spectrum is similar to that of curcuminoids, thus mimicking their colour;
- turmeric / synthetic curcuminoids.

Attempts of adulteration with synthetic products are known. These adulterations can be detected using different analytical techniques which reveal the presence of synthetic curcumin.

Another area of potential contamination is during the manufacturing process of the raw material. Quality turmeric must not contain process contaminants such as polycyclic aromatic hydrocarbons or PAHs (Reg. (EU) N. 2015/1933), pesticides (Reg. (EC) N. 396/2005) or solvents (Dir. 2009/32 / CE) outside the limits of acceptability, as prescribed by current regulations. Furthermore, it must not contain GMOs (genetically modified organisms) and must respect precise microbiological parameters.

The protocols and tools to define the quality of turmeric are therefore many and consolidated. The conscious prescription of supplements with curcumin means demanding exhaustive and transparent information from producers on quality controls and the methods by which these controls are carried out.



SAFETY

The amount of research conducted since 1815, the year in which curcumin was isolated by the French pharmacist Pelletier, makes this botanical ingredient one of the most studied in the world. Based on scientific evidence it can be stated that the safety profile of turmeric is very high.

As regards liver safety[10], curcumin has been studied all over the world for years in dozens of experimental models as a treatment for the protection of the liver against chemical damage, caused for example by alcohol abuse. In case of changes to the liver function, however, use of the product is not recommended[8].

As a general indication, it should be reiterated that botanical supplements should preferably be recommended by the doctor or pharmacist, who are able to verify the general condition of the subject, analyse any therapies or additions already in progress to evaluate possible interactions and identify the most effective dosage.

EFFICACY

Like many botanically derived substances, turmeric has poor solubility in water and is difficult to absorb by the intestine, with consequent limitation of its bioavailability.

To overcome this problem, solutions have been found that primarily concern the formulation of the supplement containing curcumin.

In this context, one of the most common formulation solutions is the association of curcumin with piperine. Piperine is a solid substance that does not dissolve in water and is able to increase the bioavailability of some nutritional substances. Piperine in combination with curcumin therefore improves the activity of the latter in the body, enhancing the amount of substance dissolved in the plasma and the extent of absorption. It should be noted, however, that piperine increases the absorption of curcumin but with a non-selective mechanism: so it may also increase the absorption of other substances, of natural or synthetic origin, foreign to an organism[9].

One of the most innovative solutions in the formulation of curcumin for helping bioabsorption is with turmeric phytosome.

The phytosome is a formulation developed by Indena to improve the bioavailability and pharmacokinetic profile of active compounds of natural origin using 100% food grade ingredients (lecithin). Lecithins are natural surfactants which, together with bile salts, participate in the physiological process of absorption of lipophilic compounds and constitute the lipid double layer of cell membranes, making compounds, not readily soluble in water, more easily absorbable for example by the intestine.

The efficacy of turmeric phytosome is demonstrated by 35 scientific studies in humans, of which at least a third were conducted with the randomized controlled scheme, relating in particular to the areas of cardiovascular, intestinal and ocular health, nutrition in sports , osteoarthritis, diabetes and the side effects of anti-cancer therapy. In these studies involving over 2000 subjects, no adverse reaction in the liver has ever been reported. Indeed, positive liver protection data have been observed and a double-blind, randomized, placebo-controlled study is ongoing in which no adverse reaction of this type has been reported to date.

Once again it is emphasised that the correct use of the botanical ingredient – which therefore includes turmeric - according to the specific indications provided by the manufacturer, is a fundamental condition for the overall safety of food supplements, as indeed of any other finished product of which it is part.

CONCLUSIONS

Botanical-based supplements are a valuable aid in maintaining people's physiological well-being, and this evidence is confirmed by the numerous published studies which demonstrate the interesting bio-medical properties of plant extracts.

"Quality" is a fundamental requirement for their safe use. In this Consensus Paper we have tried to clarify what "quality" means; this starts from the raw material of the botanical ingredient and the industrial controls applied to guarantee the product a constant phytochemical profile and titration. In addition, dedicated preclinical and clinical studies must define the biological properties and conditions of use for each specific plant ingredient.

Information on the quality of extracts of botanical origin should ideally be made available to those who prescribe, recommend and use the supplements that contain them, and that the intake of such supplements should preferably take place following the indications of doctors or pharmacists, avoiding "do-it-yourself" remedies.

Turmeric is internationally one of the most widely studied plants ever. The correct use of extracts or preparations containing this botanical ingredient is based on the specific indications that emerge from the preclinical and clinical developments of the individual products as well as on the directions of the Health authorities.

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