

## NUTRACEUTICALS AND FUNCTIONAL FOODS UNIVERSITY TASK FORCE

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## 1. UNIVERSITY TASK FORCE

University of the Naples Federico II has recently adopted a new initiative named "University Task Force" (UTF). The UTF are an effective tool to promote interdisciplinary research collaborations and to create transversal synergies between departments, creating integrations between competences and different but complementary, needful to achieve innovative goals. The UTF are also a valuable tool to stimulate and develop relationships with the territory, sharing enormous potential with research institutions, companies the great potential of both theoretical and technical skills of researchers, to activate cultural exchanges and the development of joint initiatives. At the moment the University Task Forces are five:

- ✓ Nutraceuticals and Functional Foods
- ✓ Blue Italian Growth
- ✓ Industry 4.0 and Sustainable development
- ✓ Microbiome Studies
- ✓ Polymers and Biopolymers

## 2. NUTRACEUTICALS AND FUNCTIONAL FOODS UNIVERSITY TASK FORCE

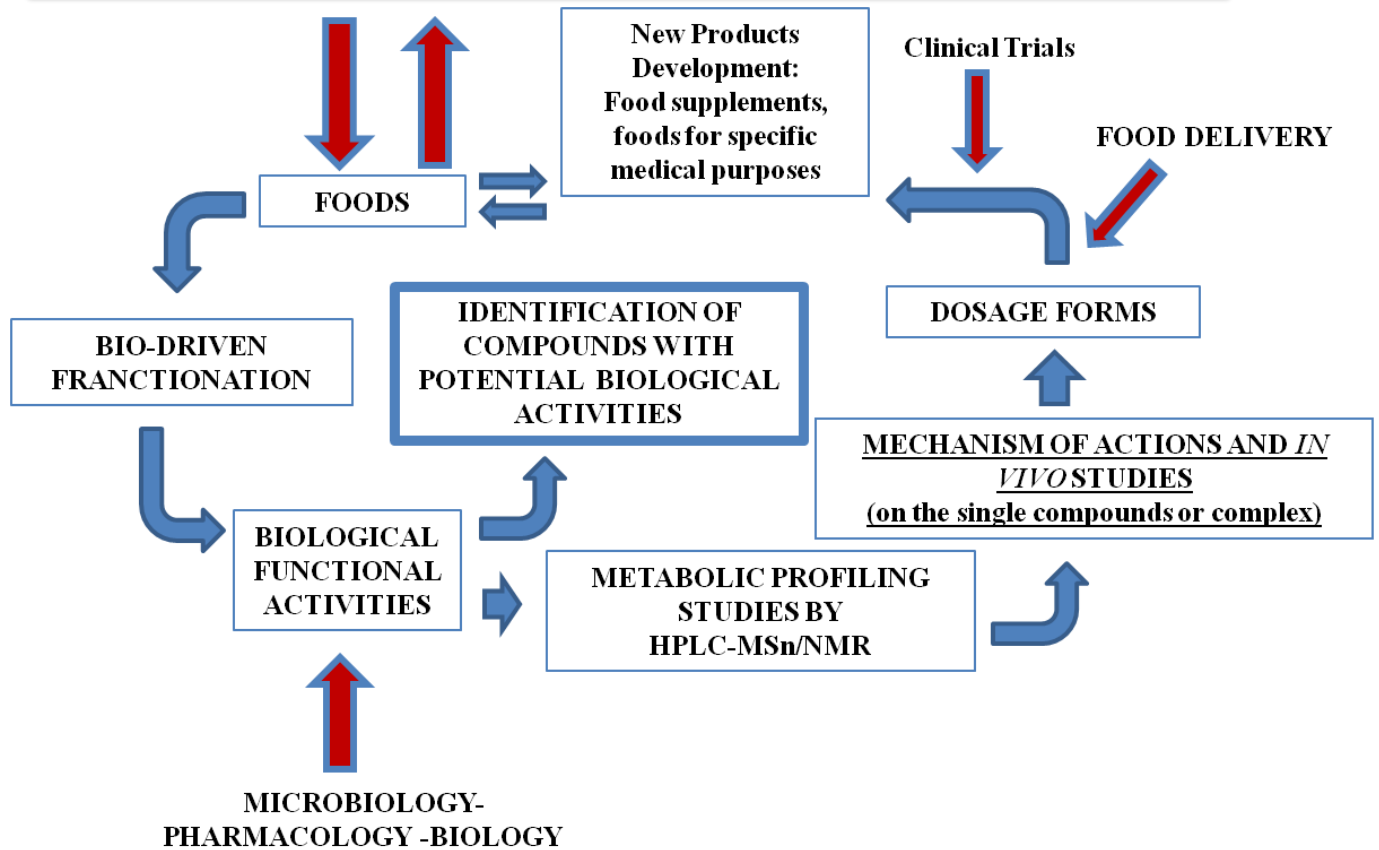
In 2018 was set up **Nutraceuticals and Functional Foods University Task Force**, with the aim to provide to health care companies in the field of the functional foods, services to help the new products development, improve the quality, guaranteeing, on a solid scientific basis, safety and effectiveness, in accordance with the reference legislation.

Multidisciplinarity of the Researcher Staff at the Pharmacy and Medicine Departments, guarantees the total coverage of the skills necessary for the research and development of innovative and high quality products, whose properties are certified by studies carried out with methodological rigour, following the current legislation and healthcare institutional guidelines.

## 3. BUSINESS SERVICES

Business services for healthcare companies cover all the stages in the production chain by the involvement of a multidisciplinary staff in the field of the chemistry, pharmaceutical technology, pharmacology, cellular and molecular biology and food law.

## NUTRACEUTICAL PROCESS



### 3.1. TECHNOLOGY TRASFER



Technology transfer of products developed in the University and especially of the Departments involved in the UTF will allow to strengthen the links between the world of research and industry.



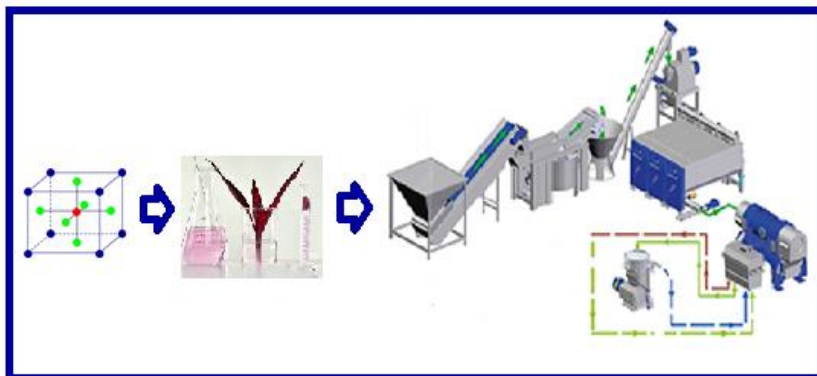
To enhance the know-how produced at the University, the knowledge on new products, deriving from the research carried out at the Departments related to UTF, obtained starting from functional foods, of both animal and vegetable origin, to be used, either as or after extraction, as ingredients of health products, will be shared with the interested companies to the aim of promoting joint projects at local, national and international level. This way provides:

- sharing information on research funding opportunities and related financial instruments (European, national and regional) with partner companies;
- supporting the drafting of research projects;
- supporting the patents registration.

### 3.2 RESEARCH AND DEVELOPMENT SUPPORT

#### 3.2.1 Identification and optimization of the extractive methodologies

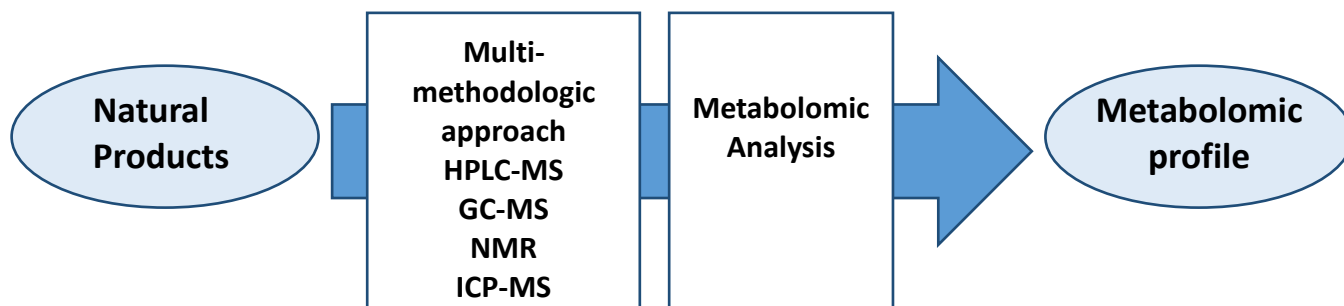
By the Design of Experiment (DoE) will optimize the extractive methods aims to enrichment the extracts of the bioactive components, using experimental approaches also applicable at industrial level to make the scale-up procedure faster and easier.



#### 3.2.2. Chemical characterization of foods and extracts

By an multi-methodologic approach with the use of advanced analytical tools such as High Performance Liquid Chromatography (HPLC), Mass spectrometry (MS), Nuclear magnetic resonance (NMR) not available in the common food analyses laboratories, is possible to define metabolic profile of the extracts to use as food ingredients, also evaluating the:

- reproducibility of the chemical composition of the extracts according to the climatic and geographical conditions of cultivation of the species from which they are obtained;
- qualitative and quantitative assessment of phytochemical markers;
- evaluation of unidentified compounds with potential toxic activity.



### 3.2.3. Development of new technologies for the functional food delivery

In the UTF there are functional food delivery laboratories where, on the basis of the ingredients constituting a food supplement, the dosage forms most compatible with the established formula can be identified and optimized, providing for the use of microencapsulated ingredients to minimize interactions with the environment and / or the other components of the product and the use of preservative or antioxidant additives according to current legislation. To evaluate the formulation feasibility can to be carry out laboratory tests and build pilot lots, in line with the critical aspects of the processes applied.

Moreover, it can be developed:

- 1) new formulations that increase the bioaccessibility and bioavailability of the compounds with nutraceutical activity to use in food supplements;
- 2) stability studies for the shelf-life of food supplements;
- 3) pharmacokinetic studies (C<sub>max</sub>, T<sub>max</sub>, AUC) of the bioactive compounds in food supplements *in vivo* and in humans models.



### 3.2.4. Preclinical studies *in vitro* and *in vivo*

The molecular and cellular laboratories of the UTF are equipped for the use of cellular and animal models reported in the scientific literature or specifically set up to identify nutraceutical properties and mechanisms of action of natural extracts and pure biomolecules.

Biological platforms today available in the UTF laboratories for the nutraceuticals cover a broad range of biological fields from leptogenic potential measurement of nutraceutical compounds until to the effect of the same on key reactions of the cellular metabolism such as glycolysis, lipogenesis and cholesterologenesis. Moreover, several mouse models of metabolic diseases and several human cell lines from gastrointestinal to neuronal, hepatic and renal ones are used. Specific biochemical tests and screening platforms have also been developed to test the effect of biomolecules on cellular energy homeostasis, growth, proliferation and differentiation status of both neoplastic and non-tumor cells.

*In vitro*, *in vivo* and *ex vivo* models for the study of innate and adaptative immune responses were also developed to study the inflammation response at the level of the gastro-intestinal tract (GI), musculoskeletal (MS) and of the nervous system central (SNC), for the study of vascular homeostasis. The laboratories have equipment **i**) for the extraction and analysis of genetic material (DNA and RNA) and PCR and RealTime PCR instruments; **ii**) for the handling of nucleic acids

(cloning, amplification and recombination of expression vectors); **iii**) for the analysis of proteins by means of biochemical tests (Western Blot), **iv**) for cellular tests (fluorescent cell counters and digital microscopes for the visualization and imaging of cell cultures); **v**) for the metabolomic analysis of cells and tissues treated with nutraceutical compounds.

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### 3.2.4. Clinical Studies

The guidelines on the studies carried out to evaluate the safety and properties of food products, drawn up by the Directorate General for Hygiene, Food Safety and Nutrition-Office IV Ex Dgsan of the Ministry of Health report that "in the food sector it is possible to carry out *in vitro*, *in vivo* experiments on animal and human models, having as object foods as defined below. These experiments must be based on a correctly formulated scientific rationale, which takes into account the type of food/ingredient/substance to be tested, and be conducted on the general principles of the Good Clinical Practice (GCP) and laboratory (Good Laboratory Practice, GLP).

So, as part of the UTF, a working group has been set up that organizes and coordinates clinical trials to demonstrate the safety and efficacy of food supplements in humans, carried out at the Cooperatives of General Practitioners. The group deals, in particular, with the preparation of documentation to be submitted to the Ethics Committees of the Cooperatives, the notification to the Ministry of Health of the clinical study, the stipulation of the insurance to cover possible risks to which the patients participating in the trial can be subject, the calculation by means of power analysis of the sample size, the definition of the type of study (randomized, controlled, in single or double blind, mono or multicentric, in parallel groups or cross-over ...), the collection of results and their statistical elaboration. The continuous comparison between the working group and General Practitioners allows to set up clinical studies taking into account the nature of the tested product that is configured as a food and not as a drug.



### 3.3. REGULATORY DECISION-MAKING COUNSELLING

#### 3.3.2. *Scientific rationales drafting and formulations monitoring*

To select the ingredients (vitamins, minerals, plant extracts and / or substances with a nutritional or physiological effect) to be used in a food supplement aimed at maintaining a certain physiological condition, a scientific rationale will be produced to justify the use of ingredients allowed by national and european legislation in the aforementioned food supplement.

In particular, we proceed with **a)** bibliographic research in the following databases of publications on the topic of the last 10 years, with more attention to those of the last 5 years (Cochrane databases, Medline, Pubmed, Scopus, Web of Science (ISI Web of Knowledge ), Science Direct, Embase), **b)** selection of publications in which the experimental work was carried out with high methodological rigour, **c)** drafting of a report with the following chapters:

- Introduction on the altered physiological state to which we want to respond with the product;
- List of ingredients that could potentially be used in the maintenance of optimal physiological conditions and indication of the mechanisms of action (if known);
- Identification of the ingredients for the new food supplement, following the literature indications.

#### 3.3.3. *Draft label monitoring and information material preparation*

The legislation in force provides precise rules for the drafting of the label of food products including food supplements. As part of the support to companies at regulatory level, the label is drafted, with the inclusion of:

- list of ingredients;
- nutritional table (which includes the calculation of the nutritional reference values to be included in the nutritional table);
- possible nutritional and /or health claims;
- others: mode of use, warnings, net weight, shelf life, storage conditions and safe use, allergens, name -address -business name of the operators.

Furthermore, on request, specific Slide KIT products can be developed for the products studied, such as leaflets, technical data sheets, brochures for the public and information material in general addressed both to consumers and professional operators, and scientific material for the training of personnel assigned to technical and scientific information of the product at the time of its placing on the market.



### ***3.3.4. Application to health claims support***

The limited number of health claims currently authorized to communicate to the consumers the biological properties of food and, in particular, food supplements, has led the UTF to organize an additional service aimed at the preparation of applications to be presented, through the Ministry of Health, to EFSA according to the guidelines issued by the European Authority for Food Safety (EFSA Journal 2017; 15 (1): 4680).

The working group involved in this activity first performs a feasibility study to verify if the health activity that must be claimed for a food supplement falls in the case of the claims of reduction of disease risk factor (according to article 14.1 of the Regulation (EC) No 1924/2006), which is considered the health claim for which is possible to demonstrate, through clinical studies conducted on healthy subjects, the efficacy of the product.

If the feasibility study indicates that the claimed effect falls into this category of claim, we proceed with the evaluation of the literature data to check if there is sufficient scientific evidence to demonstrate a cause-effect relationship between the consumption of a specific and characterized food product and the effect of reduction of a risk factor related to a disease.

If this second study also has a positive outcome, the working group proceeds with the preparation of the application which consists of the following steps:

- Part 1) Technical and administrative data
- Part 2) Characteristics of the food / constituent
- Part 3) Features of the claim
- Part 4) Identification of relevant scientific data
- Part 5) Summary of all the studies identified in Part 4
- Part 6) Attachments

## Application to health claims steps and timing



#### 4. CASE HYSTORY – "ANNURMETS"



The facilities above reported are been applied in several cases and among them, there is that of "AnnurMets" that led to the manufacture of food supplements containing an extract of apple annurca PGI (protected geographical indication) of the Campania region (Italy).

The protocol used for AnnurMets has been the following:

- 1) Selection of foods of current use, such as apple annurca, from which to produce the extract used as an ingredient of food supplements;
- 2) Chemical characterization and metabolic profile of the fruit;
- 3) Identification of the its biological-functional properties by *in vitro* and *in vivo* studies;
- 4) Identification of its biologically active components such as procyanidins, and analysis of the mechanism of action through which procyanidins carry out their biological effects;
- 5) Determination of bioaccessibility and bioavailability of active components;
- 6) Development of an industrial-scale extractive method and of an suitable formulation;
- 7) Preparation of a pilot lot for clinical trials aimed at demonstrating in humans both the safety and the health effects deriving from the consumption of the dietary supplement.

Below are reported scientific papers published on the high impact international journals attesting the studies carried out on the annurca apple, on the extract obtained from it and on the final product that are the food supplements currently on the market.





## Food Chemistry

Volume 140, Issue 4, 15 October 2013, Pages 614-622

**Nutraceutical potential of polyphenolic fractions from Annurca apple****(*M. pumila* Miller cv Annurca)****<sup>1</sup>Tenore GC, <sup>2</sup>Campiglia P, <sup>3</sup>Stiuso P, <sup>1</sup>Ritieni A, <sup>1</sup>Novellino E**<sup>1</sup>Department of Medicinal Chemistry, Università di Napoli Federico II, Via D. Montesano 49, 80131 Napoli, Italy<sup>2</sup>Department of Pharmaceutical and Biomedical Sciences, University of Salerno, Via Ponte Don Melillo, 1, 84084 Salerno, Italy<sup>3</sup>Department of Biochemistry and Biophysics, Second University of Naples, Napoli, Italy**Abstract**

The capacities of polyphenolic extracts from Annurca apple peel and flesh to inhibit the glucose and cholesterol uptake by HepG2 cells were evaluated, and compared with those of other conventional cultivars, such as Red Delicious (RD), Pink Lady (PL), Fuji (F) and Golden Delicious (GD). RD peels exhibited the best hypoglycaemic effects, while Annurca flesh appeared the most active in reducing cell cholesterol uptake among the cultivars tested. The influence of the apple polyphenolic extracts on the cell proliferation and oxidative stress was also evaluated. Particularly, RD, Annurca and PL peels decreased proliferation by a 62.5%, 48.0% and 37.5%, respectively, probably due to their prooxidant capacity. Conversely, flesh extracts appeared more protective of cells than peels: Annurca and RD, particularly, proved to be able of increasing proliferation by a 32.2% and 11.1%, respectively, probably due to their capacity of reducing cell physiological radical levels of a 33.3% and 19.9%, respectively.



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## Food Chemistry

Volume 141, Issue 4, 15 December 2013, Pages 3519-3524

**In vitro bioaccessibility, bioavailability and plasma protein interaction of polyphenols from Annurca apple (*M. pumila* Miller cv Annurca)****<sup>1</sup>Tenore GC, <sup>2</sup>Campiglia P, <sup>1</sup>Ritieni A, <sup>1</sup>Novellino E**<sup>1</sup>Department of Pharmacy, University of Naples Federico II, Via D. Montesano 49, 80131 Napoli, Italy<sup>2</sup>Department of Pharmaceutical and Biomedical Sciences, University of Salerno, Via Ponte Don Melillo, 1, 84084 Salerno, Italy**Abstract**

The in vitro bioaccessibility, bioavailability and plasma protein interaction of polyphenols from Annurca apple and other conventional cultivars were evaluated. Salivary digestion concentrated into the medium 27-35% of native apple polyphenols, suggesting the potential bioavailability through the oral mucosal epithelium of significant amounts of bioactive compounds that could be gastric sensitive and/or poorly absorbed in the intestine. Annurca flesh revealed the highest content and provided the best intestinal bioaccessibility and bioavailability of oligomeric procyanidins among all of the apple peel and flesh tested. Since 49.4% of native procyanidins were not absorbed, they are expected to accumulate in the intestinal lumen where a potential inhibition capacity of cellular cholesterol uptake could be assumed. The permeated procyanidins (6.7% of their native pattern, 12.0% of intestinal procyanidins) significantly bound (58.7%) to plasma HDLs, suggesting a major role in cholesterol metabolism. Our results would indicate Annurca apple and its potential nutraceuticals as effective in the regulation of plasma cholesterol levels.



## Food Research International

Volume 63, Part B, September 2014, Pages 252-257

**Effects of Annurca apple polyphenols on lipid metabolism in HepG2 cell lines: A source of nutraceuticals potentially indicated for the metabolic syndrome****<sup>1</sup>Tenore GC, <sup>1</sup>Calabrese G, <sup>2</sup>Stiuso P, <sup>1</sup>Ritieni A, <sup>1</sup>Giannetti D, <sup>1</sup>Novellino E**<sup>1</sup>Department of Pharmacy, Università di Napoli Federico II, Via D. Montesano 49, 80131 Napoli, Italy<sup>2</sup>Department of Biochimica, Biofisica e Patologia Generale, Second University of Naples, Napoli, Italy**Abstract**

The influence of polyphenolic extracts from Annurca apple peel and flesh on lipid metabolism in human hepatocellular liver carcinoma (HepG2) cell lines was evaluated, and compared with those of other conventional cultivars, such as Red Delicious (RD), Pink Lady (PL), Fuji (F) and Golden Delicious (GD). Annurca flesh revealed the best inhibition capacity against lipase activity, and triglyceride levels in the cell medium increased by almost 20 times above control levels. Incubation with Annurca flesh polyphenols enhanced low-density lipoproteins (LDL) receptor binding activity by 40% and led to an increase in Apolipoprotein A1 (ApoA1) cell expression of 33.3% above control levels. Experimental data would indicate for Annurca flesh polyphenols a significant hypolipidemic potential in comparison with other more common apple cultivars, thus leading to hypothesise a helpful role in the prevention and care of diseases in subjects affected by metabolic syndrome and to propose the possibility of formulating therapeutically useful nutraceutical products. Undoubtedly, further in vivo and clinical studies are needed to confirm such healthy effects through diet.





## Food Research International

Volume 76, Part 3, October 2015, Pages 466-477

**Detailed polyphenolic profiling of Annurca apple (*M. pumila* Miller cv Annurca) by a combination of RP-UHPLC and HILIC, both hyphenated to IT-TOF mass spectrometry**

**<sup>1</sup>Sommella E, <sup>1</sup>Pepe G, <sup>1</sup>Pagano F, <sup>2</sup>Ostacolo C, <sup>2</sup>Tenore GC, <sup>3</sup>Russo MT, <sup>2</sup>Novellino E, <sup>4</sup>Manfra M, <sup>1</sup>Campiglia P**

<sup>1</sup>Department of Pharmacy, University of Salerno, Via Giovanni Paolo II 132, I-84084 Fisciano, SA, Italy.

<sup>2</sup>Department of Pharmacy, University of Naples Federico II, Via D. Montesano 49, I-80131 Napoli, Italy.

<sup>3</sup>Department of Agriculture, Laboratory of Food Chemistry, University of Reggio Calabria Feo di Vito, 89100 Reggio Calabria, Italy.

<sup>4</sup>Department of Science, University of Basilicata, Viale dell'Ateneo Lucano 10, I-85100 Potenza, Italy.

**Abstract**

Annurca apple, a Southern Italian cultivar, possesses not only a particular taste and flavor, different from other types of apple, but also several healthy properties. With the aim to thoroughly elucidate the polyphenolic profile of this variety, listed as Protected Geographical Indication product, an extensive qualitative profiling of Annurca apple polyphenolic peel extract was carried out, by employing a combination of ultra high performance reversed phase (RP-UHPLC) and hydrophilic liquid chromatography (HILIC) coupled to ion trap-time of flight (IT-TOF) mass spectrometry. A total of 63 compounds were tentatively identified, 25 of which not reported in Annurca apple extract so far. Furthermore, thanks to the different selectivity obtained with the HILIC, in combination with accurate mass measurements, an improved separation and detection of procyanidins, was obtained. Moreover, the obtained profiles were compared with those of a conventional variety, such as Red Delicious (RD), highlighting their differences. This work contributes to increase the knowledge about the polyphenolic fingerprint of this typical apple variety.

## **Annurca (*Malus pumila* Miller cv. Annurca) apple as a functional food for the contribution to a healthy balance of plasma cholesterol levels: results of a randomized clinical trial**

**<sup>1</sup>Tenore GC, <sup>2</sup>Caruso D, <sup>3</sup>Buonomo G, <sup>1</sup>D'Urso E, <sup>2</sup>D'Avino M, <sup>4</sup>Campiglia P, <sup>1</sup>Marinelli L, <sup>1</sup>Novellino E**

<sup>1</sup>Department of Pharmacy, University of Naples Federico II, 80131 Naples, Italy.

<sup>2</sup>Department of Internal Medicine, Hospital Cardarelli, 80131 Naples, Italy.

<sup>3</sup>Coop. Samnium Medica, 82037 Benevento, Italy.

<sup>4</sup>Department of Pharmaceutical and Biomedical Sciences, University of Salerno, 84084 Salerno, Italy.

### **Abstract**

Recent human studies have evaluated the effect of daily apple consumption on plasma cholesterol level, which is recognized as an important risk factor for cardiovascular disease (CVD). Nevertheless, slightly significant effects have been generally registered although consuming more than two apples a day for several weeks. This study describes the influence of daily consumption of Annurca apples on the cholesterol levels of mildly hypercholesterolaemic healthy subjects. A monocentric, randomized, parallel-group, placebo-controlled, 4-month study was conducted. The subjects ( $n = 250$ ) were randomly assigned to five treatment groups (each one of 50 subjects: 28 men and 22 women). Four groups were administered one apple per day among the following: Red Delicious, Granny Smith, Fuji, Golden Delicious. The fifth group was asked to consume two Annurca apples per day, since the weight of this cultivar is on average half that of the commercial ones considered in this study. Comparing results, Annurca led to the most significant outcome, allowing a reduction in total and low-density lipoprotein cholesterol levels by 8.3% and 14.5%, respectively, and an increase in high-density lipoprotein cholesterol levels by 15.2% (all  $P < 0.001$ ). Our data would reasonably indicate Annurca apple as a useful tool to contribute to the prevention of CVD risk through normal diet.



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*J Med Food*. 2017 Mar 1; 20(3): 288–300.

PMCID: PMC5361772

Published online 2017 Mar 1. doi: [10.1089/jmf.2016.0152](https://doi.org/10.1089/jmf.2016.0152)PMID: [28296588](https://pubmed.ncbi.nlm.nih.gov/28296588/)

## A Healthy Balance of Plasma Cholesterol by a Novel Annurca Apple-Based Nutraceutical Formulation: Results of a Randomized Trial

<sup>1</sup>Tenore GC, <sup>2</sup>Caruso D, <sup>3</sup>Buonomo G, <sup>2</sup>D'Avino M, <sup>4</sup>Campiglia P, <sup>1</sup>Marinelli L, <sup>1</sup>Novellino E

<sup>1</sup>Department of Pharmacy, University of Naples Federico II, Naples, Italy.

<sup>2</sup>Department of Internal Medicine, Hospital Cardarelli, Naples, Italy.

<sup>3</sup>Coop. Samnium Medica, Benevento, Italy.

<sup>4</sup>Department of Pharmaceutical and Biomedical Sciences, University of Salerno, Salerno, Italy

### Abstract

Cardiovascular diseases are nowadays preferential targets of preventive medicine through a straightforward therapy on lipid profile. However, statins, the first-line lipid-lowering drug therapy, specifically act on low-density lipoprotein cholesterol (LDL-C), having a modest effect on plasma high-density lipoprotein cholesterol (HDL-C) concentrations. Today, a number of novel HDL-targeted therapies are emerging, along with unexpected side effects. Thus, novel and possibly safe substances, able to correct impaired lipid profile in humans, are still in great demand. Herein, based on encouraging clinical data, we formulated a nutraceutical product (AppleMetS®, AMS), based on a polyphenolic extract from Annurca apple, and demonstrated that two capsules a day of AMS, after one month, have a LDL-C lowering outcome equivalent to 40 mg of simvastatin or 10 mg of atorvastatin. Nevertheless, different from statin-based therapy, AMS exerted a notable effect on HDL (+49.2%). Based on the trial results, we can assert that AMS formulation could effectively integrate the current therapeutic arsenal to correct impaired lipid profile in humans. Specifically, AMS may be considered a complementary and/or alternative safe substance suitable for the treatment of mildly hypercholesterolemic subjects who do not present occurrence of atheromatous plaques yet.



[BMC Complement Altern Med.](#) 2017; 17: 200.

PMCID: PMC5381082

Published online 2017 Apr 5. doi: [10.1186/s12906-017-1666-7](#)

PMID: [28381226](#)

## **Annurca apple (*M. pumila* Miller cv Annurca) extracts act against stress and ageing in *S. cerevisiae* yeast cells**

**<sup>1</sup>Stirpe M, <sup>1</sup>Palermo V, <sup>1</sup>Bianchi MM, <sup>2</sup>Silvestri R, <sup>1</sup>Falcone C, <sup>3</sup>Tenore G, <sup>3</sup>Novellino E, <sup>4</sup>Mazzoni C**

<sup>1</sup>Pasteur Institute-Cenci Bolognetti Foundation, Department of Biology and Biotechnology 'Charles Darwin', Sapienza University of Rome, Piazzale Aldo Moro 5, 00185, Rome, Italy.

<sup>2</sup>Pasteur Institute-Cenci Bolognetti Foundation, Dipartimento di Chimica e Tecnologie del Farmaco, Sapienza University of Rome, Piazzale Aldo Moro 5, I-00185, Rome, Italy.

<sup>3</sup>Department of Pharmacy, University of Naples "Federico II", Naples, Italy.

<sup>4</sup>Pasteur Institute-Cenci Bolognetti Foundation, Department of Biology and Biotechnology 'Charles Darwin', Sapienza University of Rome, Piazzale Aldo Moro 5, 00185, Rome, Italy.

### **Abstract**

During the past years, a number of studies have demonstrated the positive effect of apple on ageing and different diseases such as cancer, degenerative and cardiovascular diseases. The unicellular yeast *Saccharomyces cerevisiae* represents a simple eukaryotic model to study the effects of different compounds on lifespan. We previously demonstrated that apple extracts have anti-ageing effects in this organism because of their antioxidant properties. In particular, the effect is related to the presence in this fruit of polyphenols, which give a large contribution to the antioxidant activity of apples. We used a clonogenic assay to assess the viability and the resistance to oxidative stress of *S. cerevisiae* cells in the presence of Annurca apple extracts. The production of ROS and the aberrant morphology of nuclei were detected by cell staining with the fluorescent dyes Dihydrorhodamine 123 and DAPI, respectively. Mitochondrial morphology was analyzed by following the localization of the mito-GFP protein into the mitochondrial matrix. In this study, we show that apple extracts can increase yeast lifespan, reduce the levels of reactive oxygen species and cell sensitivity to oxidative stress, and prevent nuclei and mitochondria fragmentation protecting cells from regulated cell death. In this paper, by using the yeast *S. cerevisiae* as a model, we have demonstrated that Annurca extracts possess antioxidant properties thanks to which the extracts can reduce the intracellular ROS levels and have anti-apoptotic functions thus prolonging cell lifespan. These results contribute to knowledge on the effects of natural compounds on ageing and support the use of yeast as a model organism for the development of simple tests to assess the effectiveness of bioactive substances from natural sources.



nutrients



Nutrients. 2017 Nov; 9(11): 1262.

PMCID: PMC5707734

 Published online 2017 Nov 18. doi: [10.3390/nu9111262](https://doi.org/10.3390/nu9111262)

 PMID: [29156563](https://pubmed.ncbi.nlm.nih.gov/29156563/)

## WNT Inhibitory Activity of *Malus Pumila miller* cv Annurca and *Malus domestica* cv Limoncella Apple Extracts on Human Colon-Rectal Cells Carrying Familial Adenomatous Polyposis Mutations

<sup>1</sup>Riccio G, <sup>1</sup>Maisto M, <sup>1</sup>Bottone S, <sup>1</sup>Badolati N, <sup>2</sup>Rossi GB, <sup>1</sup>Tenore GC,  
<sup>1</sup>Stornaiuolo M, <sup>1</sup>Novellino E

<sup>1</sup>Department of Pharmacy, University of Naples Federico II, 80131 Naples, Italy.

<sup>2</sup>Gastroenterology and Gastrointestinal Endoscopy Unit, Istituto Nazionale Tumori-IRCCS-Fondazione G. Pascale, 80131 Naples, Italy.

### Abstract

Inhibitors of the Wntless-related Integration site (WNT)/ $\beta$ -catenin pathway have recently been under consideration as potential chemopreventive agents against Familial Adenomatous Polyposis (FAP). This autosomal-dominant syndrome is caused by germline mutations in the gene coding for the protein APC and leads to hyperactivation of the WNT/ $\beta$ -catenin signaling pathway, uncontrolled intestinal cell proliferation and formation of adenocarcinomas. The aim of the present work was to: (i) test, on in vitro cultures of cells carrying FAP mutations and on ex vivo biopsies of FAP patients, the WNT inhibitory activity of extracts from two common southern Italian apples, *Malus pumila* Miller cv. 'Annurca' and *Malus domestica* cv 'Limoncella'; (ii) identify the mechanisms underpinning their activities and; (iii) evaluate their potency upon gastrointestinal digestion. We here show that both Annurca and Limoncella apple extracts act as WNT inhibitors, mostly thanks to their polyphenolic contents. They inhibit the pathway in colon cells carrying FAP mutations with active dilutions falling in ranges close to consumer-relevant concentrations. Food-grade manufacturing of apple extracts increases their WNT inhibitory activity as result of the conversion of quercetin glycosides into the aglycone quercetin, a potent WNT inhibitor absent in the fresh fruit extract. However, in vitro simulated gastrointestinal digestion severely affected WNT inhibitory activity of apple extracts, as result of a loss of polyphenols. In conclusion, our results show that apple extracts inhibit the WNT pathway in colon cells carrying FAP mutations and represent a potential nutraceutical alternative for the treatment of this pathology. Enteric coating is advisable to preserve the activity of the extracts in the colon-rectal section of the digestive tract.



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[J Med Food](#). 2018 Jan 1; 21(1): 90–103.

Published online 2018 Jan 1. doi: [10.1089/jmf.2017.0016](https://doi.org/10.1089/jmf.2017.0016)

PMCID: PMC5775114

PMID: [28956697](https://pubmed.ncbi.nlm.nih.gov/28956697/)

## **Annurca Apple Nutraceutical Formulation Enhances Keratin Expression in a Human Model of Skin and Promotes Hair Growth and Tropism in a Randomized Clinical Trial**

**<sup>1</sup>Tenore GC, <sup>2</sup>Caruso D, <sup>3</sup>Buonomo G, <sup>2</sup>D'Avino M, <sup>1</sup>Santamaria R, <sup>1</sup>Irace C, <sup>1</sup>Piccolo M, <sup>1</sup>Maisto M, <sup>1</sup>Novellino E**

<sup>1</sup>Department of Pharmacy, University of Naples Federico II, Naples, Italy.

<sup>2</sup>Department of Internal Medicine, Hospital Cardarelli, Naples, Italy.

<sup>3</sup>Coop. Samnium Medica, Benevento, Italy.

### **Abstract**

Several pharmaceutical products have been formulated over the past decades for the treatment of male and female alopecia, and pattern baldness, but relatively few metadata on their efficacy have been published. For these reasons, the pharmaceutical and medical attention has recently focused on the discovery of new and safer remedies. Particularly, great interest has been attracted by oligomeric procyanidin bioactivity, able to promote hair epithelial cell growth as well as to induce the anagen phase. Specifically, the procyanidin B2, a dimeric derivative extracted from apples, has demonstrated to be one of the most effective and safest natural compounds in promoting hair growth, both in vitro and in humans by topical applications. By evaluating the polyphenolic content of different apple varieties, we have recently found in the apple fruits of cv Annurca (AFA), native to Southern Italy, one of the highest contents of oligomeric procyanidins, and, specifically, of procyanidin B2. Thus, in the present work we explored the in vitro bioactivity of AFA polyphenolic extract as a nutraceutical formulation, named AppleMets (AMS), highlighting its effects on the cellular keratin expression in a human experimental model of adult skin. Successively, testing the effects of AMS on hair growth and tropism in healthy subjects, we observed significant results in terms of increased hair growth, density, and keratin content, already after 2 months. This study proves for the first time the impact of apple procyanidin B2 on keratin biosynthesis in vitro, and highlights its effect as a nutraceutical on human hair growth and tropism.



## Polyphenolic compounds and nutraceutical properties of old and new apple cultivars

<sup>1</sup>Morresi C, <sup>2</sup>Cianfruglia L, <sup>2</sup>Armeni T, <sup>2</sup>Mancini F, <sup>3</sup>Tenore GC, <sup>3</sup>D'Urso E, <sup>4</sup>Micheletti A, <sup>3</sup>Ferretti G, <sup>1</sup>Bacchetti T

<sup>1</sup>Department of Life and Environmental Sciences, Polytechnic University of Marche, Ancona, Italy

<sup>2</sup>Department of Clinical Experimental Science and Odontostomatology, Polytechnic University of Marche, Ancona, Italy

<sup>3</sup>Department of Pharmacy, University of Naples Federico II, Napoli, Italy

<sup>4</sup>Agency for Agro-food Sector Services of the Marche Region (ASSAM), Osimo, Italy

### Abstract

Aim of the study was to characterize the nutritional composition of 11 apple varieties including 9 varieties from the Regional Repertory of Biodiversity of Marche (Italy). The qualitative and quantitative profiles of polyphenols were evaluated through HPLC-DAD-MS analysis. Antioxidant properties were evaluated by 1,1-diphenyl-2-picrylhydrazyl, ferric reducing antioxidant power, and oxygen radical absorbance capacity assays. The ability of apple extracts to inhibit glyco-oxidative stress was studied using three experimental models: albumin glycated by incubation with fructose or methylglyoxal and human dermal fibroblasts incubated with high-glucose (HG) concentration. The results demonstrated a variability in polyphenolic profile, radical scavenging capacity, and ability to inhibit non-enzymatic glycation of protein. The results showed that HG treatment increased the formation of reactive oxygen species, lipid hydroperoxides, and advanced glycation end products in cells with a decrease in total antioxidant capacity. Apple extracts were able to counteract the glycoxidizing action of high glucose, the protective effect was related to apple polyphenol content. Practical applications: Local apple varieties could be considered as an important source of genes for apple breeding program and as preferable sources for the development of apple-based food with a strong focus on health beneficial effects. Information about the health-promoting components of ancient varieties may be important for the valorization and preservation of local cultivars, which may represent an important impulse to revitalize the agricultural economy in peripheral areas.





## PharmaNutrition

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**A nutraceutical formulation based on Annurca apple polyphenolic extract is effective on intestinal cholesterol absorption: A randomised, placebo-controlled, crossover study**

**<sup>1</sup>Tenore GC, <sup>1</sup>Carotenuto A, <sup>2</sup>Caruso D, <sup>3</sup>Buonomo G, <sup>2</sup>D'Avino M, <sup>1</sup>Brancaccio D, <sup>1</sup>Ciampaglia R, <sup>1</sup>Maisto M, <sup>1</sup>Schisano C, <sup>1</sup>Novellino E**

<sup>1</sup>Department of Pharmacy, University of Naples Federico II, Via D. Montesano 49, Naples, 80131, Italy

<sup>2</sup>Department of Internal Medicine, Hospital Cardarelli, Via Antonio Cardarelli, Naples, 80131, Italy

<sup>3</sup>Coop. Samnium Medica, Viale C. Colombo, 18, Benevento 82037, Italy

### Abstract

Complementary and/or alternative safe substances, able to correct impaired lipid profile in humans, are still in great demand. The objective of the present work was to evaluate the in vitro and clinical effects of a novel nutraceutical product (AMD), formulated with Annurca apple polyphenolic extracts, on the intestinal cholesterol micellar solubility. AMD was able to decrease in vitro cholesterol micellar solubility by about 85.7%, while Nuclear Magnetic Resonance experiments allowed to hypothesize dimeric procyanidins as potential responsible compounds for this effect. Then, a randomised, double blind, single centre, placebo-controlled, crossover study, was designed to evaluate the effect of AMD on the fecal cholesterol excretion. Clinical data indicated that fecal cholesterol excretion was significantly increased (about +35%) in the AMD period compared with placebo period ( $P < 0.01$ ). AMD may be regarded as a novel complementary and/or alternative safe remedy with clinical relevance in the primary cardiovascular disease prevention.



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## Annurca Apple Polyphenols Ignite Keratin Production in Hair Follicles by Inhibiting the Pentose Phosphate Pathway and Amino Acid Oxidation

<sup>1</sup>Badolati N, <sup>2</sup>Sommella E, <sup>1</sup>Riccio G, <sup>2</sup>Salviati E, <sup>3</sup>Heintz D, <sup>1</sup>Bottone S, <sup>4</sup>Di Cicco E, <sup>4</sup>Dentice M, <sup>1</sup>Tenore GC, <sup>2</sup>Campiglia P, <sup>1</sup>Stornaiuolo M, <sup>1</sup>Novellino E

<sup>1</sup>Department of Pharmacy, University of Naples Federico II. Via Montesano 49, 80149 Naples, Italy.

<sup>2</sup>Department of Pharmacy, School of Pharmacy, University of Salerno, Via Giovanni Paolo II 132, I-84084 Fisciano, Italy.

<sup>3</sup>Plant Imaging and Mass Spectrometry, Institut de Biologie Moleculaire des Plantes, CNRS, Universite de Strasbourg, 67000 Strasbourg, France.

<sup>4</sup>Department of Clinical Medicine and Surgery, University of Naples Federico II, Via Pansini 5, 80149 Naples, Italy.

### Abstract

Patterned hair loss (PHL) affects around 50% of the adult population worldwide. The negative impact that this condition exerts on people's life quality has boosted the appearance of over-the-counter products endowed with hair-promoting activity. Nutraceuticals enriched in polyphenols have been recently shown to promote hair growth and counteract PHL. *Malus pumila* Miller cv. Annurca is an apple native to Southern Italy presenting one of the highest contents of Procyanidin B2. We have recently shown that oral consumption of Annurca polyphenolic extracts (AAE) stimulates hair growth, hair number, hair weight and keratin content in healthy human subjects. Despite its activity, the analysis of the molecular mechanism behind its hair promoting effect is still partially unclear. In this work we performed an unprecedented metabolite analysis of hair follicles (HFs) in mice topically treated with AAE. The metabolomic profile, based on a high-resolution mass spectrometry approach, revealed that AAE re-programs murine HF metabolism. AAE acts by inhibiting several NADPH dependent reactions. Glutaminolysis, pentose phosphate pathway, glutathione, citrulline and nucleotide synthesis are all halted in vivo by the treatment of HFs with AAE. On the contrary, mitochondrial respiration,  $\beta$ -oxidation and keratin production are stimulated by the treatment with AAE. The metabolic shift induced by AAE spares amino acids from being oxidized, ultimately keeping them available for keratin biosynthesis.



nutrients



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 Published online 2018 Nov 20. doi: [10.3390/nu10111808](https://doi.org/10.3390/nu10111808)

 PMID: [30463345](https://pubmed.ncbi.nlm.nih.gov/30463345/)

## Annurca Apple Polyphenols Protect Murine Hair Follicles from Taxane Induced Dystrophy and Hijacks Polyunsaturated Fatty Acid Metabolism toward $\beta$ -Oxidation

<sup>1</sup>Riccio G, <sup>2</sup>Sommella E, <sup>1</sup>Badolati N, <sup>2</sup>Salviati E, <sup>1</sup>Bottone S, <sup>2</sup>Campiglia P, <sup>3</sup>Dentice M, <sup>1</sup>Tenore GC, <sup>1</sup>Stornaiuolo M, <sup>1</sup>Novellino E

<sup>1</sup>Department of Pharmacy, University of Naples Federico II. Via Montesano 49, 80149 Naples, Italy.

<sup>2</sup>Department of Pharmacy, School of Pharmacy, University of Salerno, Via Giovanni Paolo II 132, I-84084 Fisciano, Italy.

<sup>3</sup>Department of Clinical Medicine and Surgery, University of Naples Federico II, Via Pansini 5, 80149 Naples, Italy.

### Abstract

Chemotherapy-induced alopecia (CIA) is a common side effect of conventional chemotherapy and represents a major problem in clinical oncology. Even months after the end of chemotherapy, many cancer patients complain of hair loss, a condition that is psychologically difficult to manage. CIA disturbs social and sexual interactions and causes anxiety and depression. Synthetic drugs protecting from CIA and endowed with hair growth stimulatory properties are prescribed with caution by oncologists. Hormones, growth factors, morphogens could unwontedly protect tumour cells or induce cancer cell proliferation and are thus considered incompatible with many chemotherapy regimens. Nutraceuticals, on the contrary, have been shown to be safe and effective treatment options for hair loss. We here show that polyphenols from *Malus Pumila* Miller cv Annurca are endowed with hair growth promoting activity and can be considered a safe alternative to avoid CIA. In vitro, Annurca Apple Polyphenolic Extract (AAE) protects murine Hair Follicles (HF) from taxanes induced dystrophy. Moreover, in virtue of its mechanism of action, AAE is herein proven to be compatible with chemotherapy regimens. AAE forces HFs to produce ATP using mitochondrial  $\beta$ -oxidation, reducing Pentose Phosphate Pathway (PPP) rate and nucleotides production. As consequence, DNA replication and mitosis are not stimulated, while a pool of free amino acids usually involved in catabolic reactions are spared for keratin production. Moreover, measuring the effect exerted on Poly Unsaturated Fatty Acid (PUFA) metabolism, we prove that AAE promotes hair-growth by increasing the intracellular levels of Prostaglandins F<sub>2</sub> $\alpha$  (PGF<sub>2</sub> $\alpha$ ) and by hijacking PUFA catabolites toward  $\beta$ -oxidation.



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## Effect of Annurca Apple Polyphenols on Intermittent Claudication in Patients With Peripheral Artery Disease

<sup>1</sup>Tenore GC, <sup>2</sup>D'Avino M, <sup>2</sup>Caruso D, <sup>3</sup>Buonomo G, <sup>4</sup>Acampora C, <sup>5</sup>Caruso G, <sup>3</sup>Simone C, <sup>1</sup>Ciampaglia R, <sup>1</sup>Novellino E

<sup>1</sup>Department of Pharmacy, University of Naples Federico II, Via D. Montesano 49, 80131 Naples, Italy.

<sup>2</sup>Department of Internal Medicine, Hospital Cardarelli, Via Antonio Cardarelli, 80131 Naples, Italy.

<sup>3</sup>Coop. Samnium Medica, Viale C. Colombo, 18, 82037 Benevento, Italy.

<sup>4</sup>Department of Diagnostics for Images, Hospital Cardarelli, Via Antonio Cardarelli, 80131 Naples, Italy.

<sup>5</sup>Department of Emergency, Hospital Cardarelli, Via Antonio Cardarelli, 80131 Naples, Italy.

### Abstract

Peripheral arterial disease (PAD) is an atherosclerotic process involving both modifiable and nonmodifiable risk factors. Prospective cohort studies show that patients with PAD have a 6-fold greater risk of death from cardiovascular disease than those without PAD. Currently, there is no effective treatment for PAD. The study was a randomized, placebo-controlled trial, involving 180 patients, aged 35 to 75. The subjects were divided into 2 groups. One group underwent 24 weeks of nutraceutical treatment consisting in the administration of 4 capsules of Annurca apple polyphenolic extract (AMS)/day. The placebo group was administered with identically appearing capsules containing only maltodextrin. Primary outcome measures were: walking autonomy, ankle-brachial index, acceleration time. In the AMS group, at the end of the treatment period, walking autonomy was increased on average by 69% ( $p < 0.05$ ), while slighter effects were registered as regards ankle-brachial index (+25%;  $p < 0.05$ ) and acceleration time (-3.6%;  $p < 0.05$ ), when compared with baseline. Placebo group revealed no significant differences as regards variations of all outcomes measures ( $p > 0.05$ ). Our preliminary results may indicate AMS product as a promising natural and safe tool for treatment of symptoms related to PAD.



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## **Lactofermented Annurca Apple Puree as a Functional Food Indicated for the Control of Plasma Lipid and Oxidative Amine Levels: Results from a Randomised Clinical Trial**

**<sup>1</sup>Tenore GC, <sup>2</sup>Caruso D, <sup>3</sup>Buonomo G, <sup>4</sup>D'Avino M, <sup>1</sup>Ciampaglia R, <sup>1</sup>Maisto M, <sup>1</sup>Schisano C, <sup>5</sup>Bocchino B, <sup>1</sup>Novellino E**

<sup>1</sup>Department of Pharmacy, University of Naples Federico II, Via D. Montesano 49, 80131 Naples, Italy.

<sup>2</sup>Department of Internal Medicine, Hospital Cardarelli, Via Antonio Cardarelli, 80131 Naples, Italy.

<sup>3</sup>Coop. Samnium Medica, Viale C. Colombo, 18, 82037 Benevento, Italy.

<sup>4</sup>Department of Internal Medicine, Hospital Cardarelli, Via Antonio Cardarelli, 80131 Naples, Italy.

<sup>5</sup>UCCP (Unità Complessa Cure Primarie), Via Manzoni, San Giorgio del Sannio, 82100 Benevento, Italy.

### **Abstract**

Atherosclerotic cardiovascular diseases are preferential targets of healthy diet and preventive medicine partially through strategies to improve lipid profile and counteract oxidative metabolites. Ninety individuals with cardiovascular disease (CVD) risk factors were randomized (1:1:1 ratio) to three arms, according to a four-week run-in, eight-week intervention, and four-week follow up study, testing the effects of a lactofermented Annurca apple puree (lfAAP), compared to unfermented apple puree (AAP) or probiotic alone (LAB) on plasma lipid profile and trimethylamine-N-oxide (TMAO) levels. By comparing the treatments, data indicated for the subjects tested with lfAAP a higher variation of the following serum parameters, in respect to the other treatment groups: high density lipoprotein cholesterol (HDL-C), +61.8% ( $p = 0.0095$ ); and TMAO levels, -63.1% ( $p = 0.0042$ ). The present study would suggest lfAAP as an effective functional food for beneficial control of plasma HDL-C and TMAO levels.



*Nutrients*. 2019 Jan; 11(1): 163. Published online 2019 Jan 14. doi: [10.3390/nu11010163](https://doi.org/10.3390/nu11010163)

## A Boost in Mitochondrial Activity Underpins the Cholesterol-Lowering Effect of Annurca Apple Polyphenols on Hepatic Cells

<sup>1</sup>Sommella E, <sup>2</sup>Badolati N, <sup>2</sup>Riccio G, <sup>1</sup>Salviati E, <sup>2</sup>Bottone S, <sup>3</sup>Dentice M,  
<sup>1</sup>Campiglia P, <sup>2</sup>Tenore GC, <sup>2</sup>Stornaiuolo M, <sup>2</sup>Novellino E

<sup>1</sup>Department of Pharmacy, School of Pharmacy, University of Salerno, Via Giovanni Paolo II 132, I-84084 Fisciano, SA, Italy.

<sup>2</sup>Department of Pharmacy, University of Naples Federico II. Via Montesano 49, 80149 Naples, Italy.

<sup>3</sup>Department of Clinical Medicine and Surgery, University of Naples Federico II, Via Pansini 5, 80149 Naples, Italy.

### Abstract

Reduction in cholesterol blood levels represents one of the therapeutic goals to achieve in order to reduce the occurrence of cardiovascular diseases. Commonly, this goal is attempted by promoting healthy lifestyle behaviors and low-fat diets. Recently, several nutraceuticals have been shown to possess cholesterol-lowering properties and are becoming common over the counter products. Among others, apple polyphenols efficiently lower total cholesterol levels in humans and impact overall lipid metabolism. *Malus Pumila* Miller cv Annurca is an apple native to Southern Italy presenting one of the highest content of procyanidin B2, a dimeric procyanidin. Tested in clinical trials, the oral consumption of an Annurca polyphenolic extract (AAE) exerted a cholesterol-lowering effect similar to the statins Atorvastatin and Simvastatin. Despite AAE activity, the analysis of the molecular mechanism behind its cholesterol-lowering effect is unclear. Using isotope labeling and high-resolution mass spectrometry approaches we here performed a metabolic profiling of in vitro cultured human hepatocytes treated with AAE to reveal its mechanism of action. The results show that AAE acts differently than statins. The extract reprograms hepatic cell metabolism and promotes mitochondrial respiration, lipolysis and fatty acid  $\beta$ -oxidation. Citrate and acetyl-CoA, both necessary for the production of cholesterol, are diverted to the Krebs Cycle by AAE, that, ultimately, lowers cholesterologenesis and fatty acid synthesis.



## Miscellaneous

At the Nutraceuticals and Functional Foods UTF are present professors known as opinion leaders in the nutraceutical world. They provided general guidelines on the role of food supplements in maintaining well-being and health status. These scientists are engaged in the drafting of scientific rationale and guidelines for the development of new supplements.



## Nutraceuticals: Beyond the Diet Before the Drugs

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### Nutraceuticals: Beyond the Diet Before the Drugs

**Antonello Santini, Ettore Novellino**

Department of Pharmacy, University of Napoli Federico II, Naples, Italy.

#### Abstract

Diet and lifestyle are considered essential to promote and maintain the well-being as well as to prevent the onset of diseases linked to wrong lifestyle and dietary habits that can both determine pathological conditions. Many of these require pharmacological therapy; nevertheless, some can be prevented and taken care of with the use of nutraceuticals in the daily diet. Nutraceuticals are pharmacologically active substances that can be extracted from vegetal or animal food, concentrated and administered in a suitable pharmaceutical form. A nutraceutical hence is a food or part of a food that produces health beneficial effects, including the prevention and/or treatment of a disease. The proper use of these food-drugs can help to reduce and/or to slow the onset of diseases, and, in particular, all the lifestyle related health conditions, e.g. the metabolic syndrome, which is strongly depending on the improper lifestyle and incorrect dietary habit. The effectiveness of nutraceuticals can be seen with their inclusion in the daily diet as a preventive agent against the onset of disease and, therefore, beyond the diet but before the need to use a drug to treat the symptoms arising from the onset of a pathologic condition. Hypercholesterolemia, hypertension, obesity are some relevant and current examples of lifestyle related diseases for which a proper education and prevention that includes nutraceuticals in the diet is needed.



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## ALIMENTAZIONE 3.0

La nuova frontiera tra salute e sicurezza

New Business Media

Il volume raccoglie la voce di numerosi esperti in materia che - a vario titolo - concorrono ad un esame incrociato dei temi alimentari, suddivisi in due grandi partizioni: una incentrata sulla safety, qualità e controllo (matrice normativa), l'altra, più propriamente salutistica legata agli aspetti della nutrizione, degli alimenti funzionali e della nutraceutica.

In “Alimentazione 3.0 – La nuova frontiera fra salute e sicurezza”. ISBN 978-88-506-5489-5. Edagricole-Edizioni Agricole di New Business Media srl. Bologna, Italia. (2015). Cap. 8, pp. 123-136.

### Nutraceutica: la nuova frontiera tra alimenti e farmaci

**Antonello Santini, E. Novellino**

Department of Pharmacy, University of Napoli Federico II, Naples, Italy.

#### Abstract

Nutraceuticals can be used to prevent, support and treat some pathological conditions, and can be considered food-drugs, given that they possess the healing properties of natural active ingredients of recognized effectiveness, they are safe from the point of view of origin and they have a better bioavailability and tolerability compared to drugs that might, on the opposite, determine the occurrence of unwanted side effects. A nutraceutical is a food or part of a food that provides health benefits in addition to its nutritional content. Nutraceutical is, instead, the Science that studies the composition, formulation, safety, use in support of therapies and the administration of nutraceuticals, consisting of concentrated extracts of plant or are of animal origin, conveyed in the appropriate pharmaceutical form. The nutraceuticals, which can be considered food-drugs, possess in itself the healing properties of natural active ingredients of recognized efficacy. Their space of use is broad, and is positioned in the range "beyond diet, before drug" (beyond the diet but before the need to resort to the drug), and then in the large space of the own-initiative medicine, which can prevent the onset of chronic pathological conditions. There is a profound distinction between food supplements and nutraceuticals which is evident: a nutraceutical is a food (or part of a food) that produces beneficial effects for health (medicinal principle), including prevention and / or treatment of a disease. This puts nutraceuticals on the border between diet (nutrition) and drug therapy.



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## **Nutraceuticals in hypercholesterolaemia: an overview.**

**Santini A, Novellino E.**

Department of Pharmacy, University of Napoli Federico II, Naples, Italy.

### **Abstract**

Growing attention is now being given to the possible preventive/alternative ways to avoid illness onset. Changes in lifestyle and food habits are taking over from the conventional pharmaceutical-based approach, especially for chronic pathologies. Nutraceuticals have been proposed as key tools for the prevention and cure of some pathological conditions. This is leading research to develop new formulations based on these pharma-foods addressed in a specific way to prevent and cure health issues, which, in turn, will have an effect on therapy-related costs sustained by any National Health Organization. According to existing regulations, nutraceuticals cannot be categorized as either food or drugs but, by definition, often inhabit a grey area in between the two, being assimilated into food supplements, notwithstanding the beneficial properties that they can provide for some pathological conditions. A nutraceuticals-based approach for health management, in particular for some pathological conditions, has resulted in a worldwide growing ‘nutraceutical’ revolution. An outstanding example is the approach to the ‘metabolic syndrome’, which includes overweight, obesity and cardiovascular-related diseases, causing a sort of cascade of chronic health conditions, which is becoming a norm in modern life. Hypercholesterolaemia is one of these. It represents an example of a pathology that can be linked to both a poor lifestyle and dietary habits. The nutraceutical approach to hypercholesterolaemia is described in the present review as a possible alternative to the conventional drug-based therapy.



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## Nutraceuticals: A paradigm of proactive medicine

**Santini A, Tenore GC, Novellino E.**

Department of Pharmacy, University of Napoli Federico II, Via D. Montesano, 49-80131 Napoli, Italy.

### Abstract

Nutraceuticals define a new category which shades the frontier between drugs and food. As per its definition, a nutraceutical is "a food or part of a food that provides benefits health in addition to its nutritional content". Active substances either way extracted from plants (phytochemicals) or of animal origin, when extracted, concentrated and administered in a suitable pharmaceutical form, can create a very promising toolbox useful to prevent and/or support the therapy of some pathologic conditions given their proven clinical efficacy. It is worldwide recognized that diet and lifestyle are essential to promote and maintain well-being and nice-being condition, other than help to prevent diseases possible onset. Both non-correct dietary habits and lifestyle can in fact determine pathological conditions. The metabolic syndrome, a worldwide epidemic threat, can be named an outstanding example. This syndrome is characterized by a cascade of cardio metabolic risk factors which include obesity, insulin resistance, hypertension, and dyslipidemia. Prevention is the key strategy for an effective proactive medicine, in which efforts are addressed to prevention and, consequently, to lower the risk connected to some lifestyle related diseases reducing, at the same time, any National Health Systems cost needed to guarantee the proper therapeutic approach based on pharmaceuticals. Nutraceuticals use in prevention is a proactive reverse approach tool to pre-clinical health conditions. They can be effectively used, by including in the daily diet, in an area which shades in the range "beyond the diet, before drugs", since they combine both nutritional and beneficial healthy properties of food extracts with the healing properties of natural active compounds.

*Editorial*

Foods. (2017). 6 (9), 74. <http://dx.doi.org/10.3390/foods6090074>

**To Nutraceuticals and Back: Rethinking a Concept**

**Antonello Santini, Ettore Novellino**

Department of Pharmacy, University of Napoli Federico II, Via D. Montesano, 49-80131 Napoli, Italy.

**Abstract**

The concept of nutraceuticals as pharma-foods comes from far. This term is made from the two words “nutrient” and “pharmaceutical”, was coined by Stephen De Felice, and is defined as “a food or part of a food that provide medical or health benefits, including the prevention and/or treatment of a disease”.

This definition leads to a partial overlap with the definition of a food supplement. In fact, both claim beneficial effects for health; however, while nutraceuticals are made from food or part of a food, food supplements are single substances used alone or in mixtures with the scope of adding micronutrients when the body is in need of them.

## Annals of Pharmacology and Pharmaceutics

Short Communication  
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### Nutraceuticals, food supplements and cholesterol level control

**A. Santini, E. Novellino**

Department of Pharmacy, University of Napoli Federico II, Via D. Montesano, 49-80131 Napoli, Italy.

#### Abstract

It should be made a clear distinguish between dietary supplements and nutraceuticals. There is lack of information on the definition and use of food matrices, functional foods, probiotics, herbal products, and food derived products which claim beneficial health effect but is often not supported by scientific data. On the opposite, nutraceuticals efficacy must be supported by clinical evidences. Increasing interest in nutraceuticals, dietary supplements, functional foods, etc., it is related to the growing awareness that the use of drugs may have undesirable side effects that may compromise or limit a long-term use.

A nutraceuticals is a food or part of a food, concentrated and administered in the appropriate pharmaceutical form, which provides clinically verified health benefits. Unfortunately, there is not yet a shared regulation defining the nutraceuticals as a new category within the area of food derived products.



## REVIEW

**Nutraceuticals: opening the debate for a regulatory framework****Santini A<sup>1</sup>, Cammarata SM<sup>2</sup>, Capone G<sup>2</sup>, Ianaro A<sup>1</sup>, Tenore GC<sup>1</sup>, Pani L<sup>3</sup>, Novellino E<sup>1</sup>.**<sup>1</sup> Department of Pharmacy, University of Napoli Federico II, Via D. Montesano, 49 -, 80131, Naples, Italy.<sup>2</sup> AIFA - Agenzia Italiana del Farmaco, Via del Tritone, 181 -, 00187, Rome, Italy.<sup>3</sup> Department of Psychiatry and Behavioral Sciences, University of Miami, School of Medicine, 33136-1015, Miami, FL, USA.**Abstract**

Currently, nutraceuticals do not have a specific definition distinct from those of other food-derived categories, such as food supplements, herbal products, pre- and probiotics, functional foods, and fortified foods. Many studies have led to an understanding of the potential mechanisms of action of pharmaceutically active components contained in food that may improve health and reduce the risk of pathological conditions while enhancing overall well-being. Nevertheless, there is a lack of clear information and, often, the claimed health benefits may not be properly substantiated by safety and efficacy information or in vitro and in vivo data, which can induce false expectations and miss the target for a product to be effective, as claimed. An officially shared and accepted definition of nutraceuticals is still missing, as nutraceuticals are mostly referred to as pharma-foods, a powerful toolbox to be used beyond the diet but before the drugs to prevent and treat pathological conditions, such as in subjects who may not yet be eligible for conventional pharmaceutical therapy. Hence, it is of utmost importance to have a proper and unequivocal definition of nutraceuticals and shared regulations. It also seems wise to assess the safety, mechanism of action and efficacy of nutraceuticals with clinical data. A growing demand exists for nutraceuticals, which seem to reside in the grey area between pharmaceuticals and food. Nonetheless, given specific legislation from different countries, nutraceuticals are experiencing challenges with safety and health claim substantiation.



## Expert Review of Clinical Pharmacology

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## Nutraceuticals: shedding light on the grey area between pharmaceuticals and food

**Santini A, Novellino E.**

Department of Pharmacy , University of Napoli Federico II , Napoli , Italy.


### Abstract

The term ‘nutraceutical’, originally coined in 1989 by Stephen DeFelice, founder and chairman of the Foundation for Innovation in Medicine is a portmanteau of the words ‘nutrition’ (indicating a nourishing food or food component) and ‘pharmaceutical’ (with reference to a drug), the concept of nutraceutical and its potential has been described and widely assessed in the following years since 1995. It identifies a food or part of a food, which can be of vegetal or animal origin, and has a potential pharmaceutical activity. Food is the source of nutrients (macro and micro) for the body metabolism. In some circumstances, however, there is the lack of some of them so to require the addition to the regular diet of food supplements. These last are food-derived products which can compensate and/or can have a beneficial effect on health due to the addition of specific components (minerals, vitamins, etc.) if there is a lack of them in daily diet. Food supplements may not have any proven pharmacological effect. On the opposite, nutraceuticals should have proven health beneficial effect as a requirement.



## Expert Opinion on Therapeutic Patents

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### A decade of nutraceutical patents: where are we now in 2018?

**Patricia Daliu, Antonello Santini , Ettore Novellino**

Department of Pharmacy , University of Napoli Federico II , Napoli , Italy.

#### Abstract

In the last 10 years, nutraceuticals have grown in interest to researchers, industry, and consumers and are now familiar in the collective imagination as a tool for preventing the onset of a disease. Often nutraceuticals are confused with biologically active phytochemicals/botanicals which can have health benefits. This is a misunderstanding however as the term nutraceutical refers to a product that must have a beneficial effect on health proven by clinical testing. Areas covered: A search has been performed on both recent patents and the literature regarding nutraceuticals focusing on the beneficial and proven health effects on pathological conditions to give an overview of the state-of-the-art developments in this area. Patents and literature data addressing specific pathological conditions are discussed. Expert opinion: Nutraceuticals represent a challenge for the future of drug-based pharmacotherapy, and, at the same time, are a powerful tool for the prevention of chronic disease. They are not proposed as an alternative to drugs, but instead, can be helpful to complement a pharmacological therapy and prevent the onset of chronic diseases in subjects who do not qualify for conventional pharmacological treatment.



Expert Rev Clin Pharmacol. 2019 Jan;12(1):1-7. doi: 10.1080/17512433.2019.1552135. Epub 2018 Nov 30.

**From pharmaceuticals to nutraceuticals: bridging disease prevention and management.**  
**Daliu P, Santini A, Novellino E.**

Department of Pharmacy , University of Napoli Federico II , Napoli , Italy.

**Abstract**

Nutraceuticals, up today, do not have a specific definition distinct from those of other food-derived categories, e.g. food supplements, herbal products, pre and probiotics, functional foods, etc. They have, however, a pharmacological beneficial effect on health. Many studies have been recently addressed to assess their safety, efficacy, and regulation since they are getting growing attention by market and research, with the aim to clear the difference between them and other market available food-derived products that claim beneficial effect on health. Areas covered: The understanding of the potential mechanisms of action of pharmaceutically active substances contained in nutraceuticals that may improve health and reduce the risk of pathological conditions while enhancing overall well-being is the challenge for nutraceuticals to be considered as a preventive and therapeutic efficient tool in facing some diseases. Expert commentary: It is of utmost importance to have a proper and unequivocal definition of nutraceuticals and a shared regulation. Nevertheless, there is a lack of clear information and, often, the claimed health benefits may not be properly substantiated by safety and by efficacy in vivo data, which can induce false expectations and miss the target for a product to be effective, as claimed.



Curr Pharm Biotechnol. 2015;16(3):265-71.

## Exploring the Nutraceutical Potential of Polyphenols from Black, Green and White Tea Infusions – An Overview

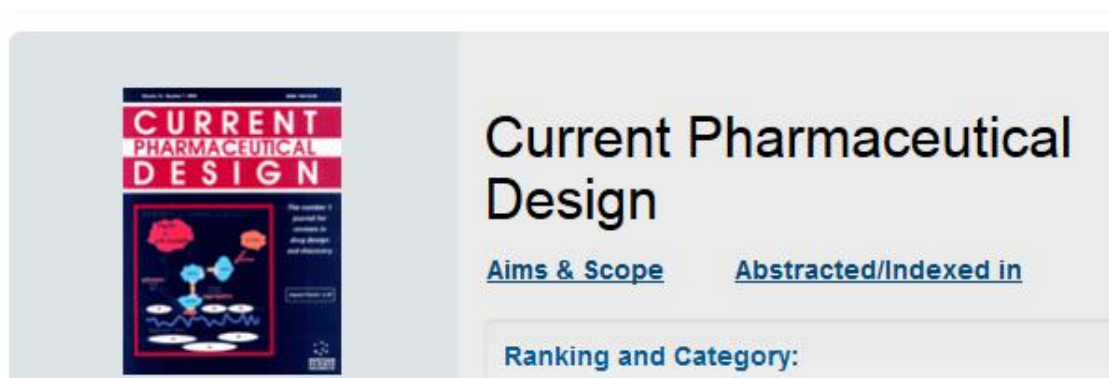
<sup>1</sup>G.C. Tenore, <sup>2</sup>M Daglia, <sup>1</sup>R Ciampaglia, <sup>1</sup>E Novellino.

<sup>1</sup>Department of Pharmacy, University of Naples Federico II, Via D. Montesano 49, 80131 Napoli, Italy;

<sup>2</sup>Department of Drug Sciences, University of Pavia, Via Taramelli 12, 27100 Pavia, Italy

### Abstract

Black, green, and white teas are the main commercial teas obtained from buds and leaves of *Camellia sinensis* (L.). The postharvest processing treatments, together with genotype and growing techniques, may strongly affect the chemical composition of the tea infusion and, thereby, its potential effects on health. Catechins constituted up to 30% of tea leaves dry weight. During fermentation, polyphenols undergo enzymatic oxidation, leading to the formation of condensed polymeric compounds regarded as responsible for the typical organoleptic properties of black tea leaves and related infusions. Scientific studies has been recently focusing on the possibility that tea polyphenols, particularly those of black and green tea, may lead to healthy properties in individuals affected by diseases correlated to metabolic syndrome. In vivo experiments reveal that green and black tea polyphenols may be able to reduce hyperglycemia and insulin resistance. Other works suggest that black tea polymeric products may be effective in decreasing blood cholesterol levels and hypertriacylglycerolemia. To this regard, very few data about white tea, being the rarest and the least handled tea, are available so far. It has been reported that white tea could show higher antioxidative capacity than green tea and to exert in vitro lipolytic activity. Considering the increasing interest towards healthy potential through diet and natural medicaments, the aim of the present review was to overview the nutraceutical potential of polyphenols from tea after various degrees of fermentation.



Curr Pharm Des. 2017;23(17):2474-2487.

## Effects of Tea and Coffee Consumption on Cardiovascular Diseases and Relative Risk Factors: An Update.

**Di Lorenzo A<sup>1</sup>, Curti V<sup>1</sup>, Tenore GC<sup>2</sup>, Nabavi SM<sup>3</sup>, Daglia M<sup>4</sup>.**

<sup>1</sup> Department of Drug Sciences, Medicinal Chemistry and Pharmaceutical Technology Section, University of Pavia, Via Taramelli 12, 27100, Pavia, Italy.

<sup>2</sup> Department of Pharmacy, University of Naples Federico II, Via D. Montesano 49, 80131 Napoli, Italy.

<sup>3</sup> Applied Biotechnology Research Center, Baqiyatallah University of Medical Sciences, P.O. Box 19395-5487, Tehran, Iran.

<sup>4</sup> Department of Drug Sciences, Pavia University, 27100, Pavia, Italy.

### Background

Tea and coffee are the second and third most consumed beverages after water, respectively. The high consumption of these beverages is due to the sensorial properties and effects on psychological and physiological functions, induced by caffeine and many other bioactive components responsible for the protective effects on human health generally ascribed to these beverages.

### Methods

The goal of this review article is to collect the scientific data obtained from clinical trials published in the last five years on the role of tea and coffee consumption against cardiovascular diseases (CVDs) and CVD risk factors such as hypertension, hyperglycemia, and hyperlipidaemia.

### Results

In normal weight subjects, clinical trials showed that the consumption of tea is inversely associated to CVD risk factors or no association was found. Differently, in overweight subjects, the clinical trials and the metaanalyses showed an inverse correlation between tea consumption and CVDs. As regards coffee, it has long been suspected to be associated to high risk of CVDs. Nevertheless, some recent investigations reported that moderate coffee consumption have no effect or even protective

effects against CVDs risk factors. The results of the metaanalyses confirm this trend suggesting that moderate coffee drinkers could be associated to a lower risk of CVDs than non- or occasional coffee drinkers or no association can be demonstrated between coffee consumption and CVDs.

**Conclusion**

Literature data on tea consumption and CVD risk factors support that tea consumption reduces some risk factors especially in overweight people and obese subjects. Therefore, these results seem to suggest that tea could exert a protective effects against CVD development. As regards coffee, the results are controversial and did not allow to draw conclusions. Therefore, further research is needed before definitive recommendations for coffee consumption against CVD development can be made.



Curr. Pharm. Biotechnol. 2014 15(4): 298-303.

## Tea consumption and risk of ischemic stroke: a brief review of the literature.

<sup>1</sup>Nabavi SM, <sup>2</sup>Daglia M, <sup>1</sup>Moghaddam AH, <sup>1</sup>Nabavi SF, <sup>2</sup>Curti V

<sup>1</sup>Department of Biology, Faculty of Basic Sciences, University of Mazandaran, Babolsar, Iran

<sup>2</sup>Department of Drug Sciences, Medicinal Chemistry and Pharmaceutical Technology Section, University of Pavia, Via Taramelli 12, 27100, Pavia, Italy

### Abstract

Stroke is an important cerebrovascular disease which causes chronic disability and death in patients. Despite of its high morbidity and mortality, there are limited available effective neuroprotective agents for stroke. In recent years, the research aimed at finding novel neuroprotective agents from natural origins has been intensified. *Camellia sinensis* L. (tea) is the second most consumed beverage worldwide, after water. It is classified into green and white, oolong, black and red, and Pu-erh tea based on the manufacturing process. Catechins are the main phytochemical constituents of *Camellia sinensis* which are known for their high antioxidant capacity. On other hand, it is well known that oxidative stress plays an important role in the initiation and progression of different cardiovascular diseases such as stroke. Therefore, the present article is aimed to review scientific studies that show the protective effects of tea consumption against ischemic stroke.





## Influence of in vitro simulated gastroduodenal digestion on the antibacterial activity, metabolic profiling and polyphenols content of green tea (*Camellia sinensis*)

A Marchese<sup>a</sup>; E Coppo<sup>a</sup>; A.P.Sobolev; <sup>b</sup>D Rossi; <sup>c</sup>L Mannina<sup>db</sup>M Daglia<sup>c</sup>

<sup>a</sup>Microbiology Unit DISC, University of Genoa, Largo R. Benzi, 10, 16132 Genoa, Italy

<sup>b</sup>Istituto di Metodologie Chimiche, Laboratorio di Risonanza Magnetica “Annalaura Segre”, CNR, I-00015 Monterotondo, Rome, Italy

<sup>c</sup>Department of Drug Sciences, Medicinal Chemistry and Pharmaceutical Technology Section, Pavia University, Via Taramelli 12, 27100 Pavia, Italy

<sup>d</sup>Dipartimento di Chimica e Tecnologie del Farmaco, Sapienza Università di Roma, Piazzale Aldo Moro 5, I-00185 Rome, Italy

### Abstract

The antistaphylococcal activity as well as the metabolic profiling and polyphenols content of green tea (*Camellia sinensis*) before and after in vitro simulated gastric, duodenal and gastroduodenal digestion were investigated. Gastric and duodenal digested samples showed antistaphylococcal activity, whereas gastroduodenal digested samples did not show any antibacterial activity. Metabolite analysis, carried out using an explorative untargeted NMR-based approach and a RP-HPLC-PAD-ESI-MSn method, showed that green tea polyphenols are stable under gastric conditions. Duodenal digested sample maintained the antibacterial activity, even if some polyphenols are widely degraded. Epicatechin 3-gallate, under duodenal digestive conditions, is hydrolyzed to produce epicatechin, whereas epigallocatechin 3-gallate reacts with digestive enzymes and a galloyl-high molecular weight derivative is produced. Gastroduodenal digestion results in degradation of polyphenols, especially gallocatechins, considered the main responsible for the antibacterial activity. These results explain the loss of activity of gastroduodenal digested samples and why in vivo green tea has neither protective nor therapeutic effects against intestinal and systemic bacterial infections.

## Molecular Nutrition & Food Research

Mol Nutr Food Res. 2016 Mar;60(3):566-79. doi: 10.1002/mnfr.201500567. Epub 2015 Dec 29

### Antidepressive-like effects and antioxidant activity of green tea and GABA green tea in a mouse model of post-stroke depression

Di Lorenzo A<sup>1</sup>, Nabavi SF<sup>2</sup>, Suredda A<sup>3</sup>, Moghaddam AH<sup>4</sup>, Khanjani S<sup>4</sup>, Arcidiaco P<sup>5</sup>, Nabavi SM<sup>2</sup>, Daglia M<sup>1</sup>

<sup>1</sup>Department of Drug Sciences, Medicinal Chemistry and Pharmaceutical Technology Section, Pavia University, Viale Taramelli 12, Pavia, Italy.

<sup>2</sup> Applied Biotechnology Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran.

<sup>3</sup> Grup de Nutrició Comunitària i Estrès Oxidatiu (IUNICS) and CIBEROBN (Physiopathology of Obesity and Nutrition) Universitat de les Illes Balears, Palma de Mallorca, Spain.

<sup>4</sup> Department of Biology, Faculty of Basic Sciences, University of Mazandaran, Iran.

<sup>5</sup> Centro Grandi Strumenti, University of Pavia, Pavia, Italy.

#### Abstract

##### Scope

Growing evidence suggests that oxidative stress plays a role in the development of chronic diseases such as cardiovascular disease and some psychiatric disorders. Tea consumption exerts beneficial effects against damage induced by cerebral ischemia-reperfusion in ischemic stroke and depressive symptoms in depression. The aim of this study was to evaluate, *in vivo*, the protective activity of green tea (GT) and GABA green tea (GGT) against post-stroke depression (PSD), a common consequence of stroke.

##### Methods and Results

The antidepressive-like effects of GT and GGT were determined by behavioral tests in a mouse model of post-stroke depression. The antioxidant activity was evaluated by GSH, SOD, and TBARS measurements on mouse brain. The chemical composition of tea extracts was characterized through chromatographic methods. GGT and GT resulted active in the modulation of depressive symptoms and the reduction of oxidative stress, restoring normal behavior, and at least in part, antioxidant endogenous defenses. The higher polyphenol, theanine, glutamine, and caffeine content may justify the higher activity found in GGT.

##### Conclusions

This work represents the first attempt to demonstrate the positive effect of tea, and especially GGT, on post-stroke depression and to correlate this effect with the antioxidant activity and phytochemical composition of tea.



## Improvement of Antioxidant Defences and Mood Status by Oral GABA Tea Administration in a Mouse Model of Post-Stroke Depression

Maria Daglia,<sup>1</sup> Arianna Di Lorenzo,<sup>1,2</sup> Seyed Fazel Nabavi,<sup>3</sup> Antoni Sureda,<sup>4</sup> Sedigheh Khanjani,<sup>5</sup> Akbar Hajizadeh Moghaddam,<sup>6</sup> Nady Braidy,<sup>7,8</sup> and Seyed Mohammad Nabavi<sup>3</sup>

<sup>1</sup>Department of Drug Sciences, Medicinal Chemistry and Pharmaceutical Technology Section, Pavia University, Viale Taramelli 12, 27100 Pavia, Italy;

<sup>2</sup>KOLINPHARMA S.p.A., Lainate, Corso Europa 5, 20020 Lainate (MI), Italy

<sup>3</sup>Applied Biotechnology Research Center, Baqiyatallah University of Medical Sciences, P.O. Box 19395-5487, Tehran 19395-5487, Iran;

<sup>4</sup>Grup de Nutrició Comunitària i Estrès Oxidatiu and CIBEROBN (Physiopathology of Obesity and Nutrition), Universitat de les Illes Balears, Palma de E-07122 Mallorca, Spain;

<sup>5</sup>Department of Physiology, Faculty of Biological Sciences, Shahid Behshti University, P.O. Box 19615-1178, Tehran 19615-1178, Iran;

<sup>6</sup>Department of Biology, Faculty of Basic Sciences, University of Mazandaran, 47416-95447 Babolsar, Iran;

<sup>7</sup>Centre for Healthy Brain Ageing, School of Psychiatry, University of New South Wales, Sydney, NSW 2052, Australia;

<sup>8</sup>CHeBA NPI, Euroa Centre, Prince of Wales Hospital, Barker Street, Randwick, NSW 2031, Australia

### Abstract

Green GABA (GGABA) and Oolong GABA (OGABA) teas are relatively new varieties of tea, whose chemical composition and functional properties are largely under-studied, despite their promising health capacities. Post stroke depression (PSD) is a complication of stroke with high clinical relevance, yielding increasing mortality and morbidity rates, and a lower response to common therapies and rehabilitation. **Methods:** Two chemically characterized commercial samples of GGABA and OGABA were investigated for effects on mood following oral administration using a mouse model of PSD, through common validated tests including the Despair Swimming Test and Tail Suspension Test. Moreover, the antioxidant activity of GGABA and OGABA was evaluated by determining the levels of lipid peroxidation products and the activity of antioxidant enzymes in the mouse brain in vivo. **Results:** GGABA and OGABA attenuated depressed mood by influencing behavioral parameters linked to depression. GGABA was more active than OGABA in this study, and this effect may be likely due to a higher content of polyphenolic substances and amino acids in GGABA compared to OGABA. GGABA also exerted a greater antioxidant activity. **Conclusions:** Our data suggests that GABA tea is a promising candidate that can be used as an adjuvant in the management of PSD.