ACTA SCIENTIFIC NUTRITIONAL HEALTH (ISSN:2582-1423)

Volume 4 Issue 1 January 2020

Review Article

Phytochemicals Between Nutrition and Medicine

Grzegorz Grynkiewicz*

Łukasiewicz Research Network; Pharmaceutical Research Institute, Warszawa, Poland

***Corresponding Author:** Grzegorz Grynkiewicz, Pharmaceutical Research Institute, Warszawa, Poland. **E-mail:** g.grynkiewicz@ifarm.eu.

Received: November 18, 2019; **Published:** December 05, 2019

DOI: 10.31080/ASNH.2020.04.0564

Abstract

In the past structural diversity of natural products have inspired mainly organic and medicinal chemists, looking for new pharmacophoric fragments useful for design of novel drugs. Ethnopharmacology and its more recent advanced form – pharmacognosy, classified plants into poisonous and curative categories, but practically neglected chemical components of plants cultivated for food and feed. Contemporary life sciences drawing from newly acquired knowledge of genomics, genetic engineering, and systems biology, have largely changed traditional landscape of strictly divided disciplines and fields of science. Fading borders between natural product chemistry, pharmacology, biochemistry and nutrition sciences, call for a new look at renewable biological resources and designing most rational way of their exploitation. In particular, beside cultivated medicinal plants, from which active pharmaceuticals are isolated with due care, other kinds of biomass including agricultural crops, spices, vegetables and fruits, should be looked at as multipurpose raw materials, which contain some valuable phytochemicals, compounds of considerable potential for improving human health and well-being.

Keywords: Natural Products; Plant Metabolites; Plant Phenolics; Flavonoids; Health Benefits; Chemoprevention

Introduction

Chemical compounds of natural origin (natural products, secondary metabolites) were essential for ethnomedicinal tradition since the time immemorial but their modern perception, (including structure elucidation, analytical specifications, study of pharmacological activity and elaboration of clinical indications), which started with advent of organic chemistry in XIXth century, tends to evolve continuously with accumulation of new scientific knowledge within life sciences field [1-4]. For many decades the awe of natural products structural diversity turned nearly entire research effort towards new drug discovery [5,6]. Recent discoveries in biology, particularly genomics, genetic engineering, metabolomics, and epigenetics, have dramatic consequences on understanding life, our environment and its significance for human health. It has been realized that continuous exposure (or lack of it) of our physiology to enormous variety of non-caloric constituents of plant derived food, is of great importance in terms of pharmacological and possibly also toxicological effects. New biology (systems biology), after two ages of reductionism, describes life with focus on molecular level, as dynamic networks of biochemical processes, assembled in cellular and organismal systems, which are equipped with metabolic functions and ability to multiply. Structure and functions of biological systems are currently being studied principally in terms of molecular biology, collecting data and evidence how biological diversity, expressed chemically in form of individual metabolome diversity, can interact at systemic level [7,8]. In this respect, traditional divide between biology and chemistry as the "two cultures" is over, since principal tools of research and methods of experimental data management became the same in both fields. Our current awareness of natural product functions as constituents of food, medicinal plants, dietary supplements, nutraceuticals, and phytopharmaceuticals, is strongly influenced not only by the state of scientific knowledge stemming from pharmacognosy, but also by such global factors as market trends and appreciation of the need for implementation of circular bioeconomy. Last but not least, appearance of rapidly growing class of health conscious users of herbal products and phytochemicals who use open source scientific information becomes of importance. These well-educated and informed customers, seeking commercial health promoting materials other than prescription and OTC drugs, and relying in their choices on factual credibility rather than superficial advertisement, become a social force with potential influence on independent media opinion, with some far reaching consequences.

Nutraceuticals: assignments and attributions

Towards the end of the last century many new concepts concerning human health have emerged from the mainstream biological science research, most of them related to influence of xenochemicals on human physiology and pathology. The idea of chemoprevention was first formulated by MB Sporn in 1978, in connection with cancer preventive activity of some carotenoids [9] and its appreciation, despite of some uncertainties during clinical trials, has attained the level of National Cancer Institute Chemoprevention Program during early 1990-ties [10]. Initially concentrated on vitamin A and its analogs, chemoprevention studies spread over all categories of secondary metabolites and gradually extended to inhibitory effects towards ailments other than cancer, particularly of chronic degenerative diseases [11,12]. These studies became instrumental not only in researching mechanism of cancer biology, neurodegeneration, and other pathologies of multifactorial origin but significantly contributed to all areas of natural products pharmacology, identifying a plethora of new drug leads and candidates [13,14]. Another idea which immensely influenced development of herbal materials as marketable products came from DeFelice, who coined up the term "nutraceuticals" in 1995, for compounds of natural origin with potential of improving human health when used as food ingredients [15,16]. In original wording nutraceutical is "any substance that may be considered a food or part of a food and provides medical or health benefits, including the prevention and treatment of disease". This was often interpreted as a plain suggestion the nutraceuticals are actually isolates from food Such description has evoked many problems; it seems to work reasonably well for market analyses but it defies attempts to establish legally binding definition of products as well as their classification and specifications [17,18]. Nevertheless, popularity of the term is overwhelming, as evidenced by over 500 related publications appearing in scientific literature annually in recent years. Heterogeneity of the nutraceutical category, which spans from medicinal products applied for treatment of well described deficiencies (vitamins, enzymes and minerals), through nutrients such as amino acids and lipids, primary and secondary metabolites, cultures of probiotic bacterial strains (Lactobacillus, Bifidobacterium, etc.), to therapeutic peptides such as vaccines or antibodies, produced in transgenic plants or other genetically modified organisms, makes it difficult to establish common scientific criteria for specification and application. This applies in the first place to the safety considerations, since incidence of inefficiency, unwanted effects, adulteration etc., have very different statistics and consequences in various sub-categories [19,20]. Additionally, nutraceutical category is a subject to further derivatization, giving rise to functional foods, health foods, fortified foods, designer foods, botanical foods, molecular foods, etc., and relations of these terms to already established dietary supplements remains less than clear. The food connection is a strong determinant towards commercialization, and business connotation is often perceived as a factor opposing open science and open innovation principles. The market value reports and estimates indicate that already in 2010 the US nutraceuticals trade topped $ 50 bln., followed by EU with $ 35 bln. value and Japan ($ 27.7 bln.) with figure similar to the rest of Asia, while annual growth rates in range 6 – 8% were predicted. It is likely that some fraction of nutraceutical business is counted as foods, for which the trade volume is at least one order of magnitude higher. Literature searches indicate clearly that excellent quality academic research, totally independent from market forces, exists and brings new essential data on biological and pharmacological activity of chemical compounds of plant origin, often mentioned in tables and reviews devoted to nutraceuticals. Examples can be find in the most epidemiologically significant areas as cancer, metabolic syndrome and neurodegeneration [21-26]. In research on healthy food ingredients, just as in research on chemoprevention, reference is often made to phytochemicals, as biologically active non-nutrients present in food as a result of plant metabolic activity [1,3,14,16]. A very interesting case of a healthcare product design and development, based on commercially available phytochemical substances (berberine; folic acid; astaxanthin and coenzyme Q10; registered name of the cholesterol lowering preparation: Armolipid Plus), carried out as a multicenter international scientific cooperation and successfully validated in a clinic was recently described [27], demonstrating wide span of innovative opportunities. The term phytochemical in a structural sense covers all branches of plant secondary metabolism and in functional sense can accommodate various categories of biologically active materials such as phytomedicinal compounds (drug active substances), vitamins, enzyme inhibitors, nutraceuticals, antioxidants, chemoprotectants, immuno-enhancers and immuno-modulators, as well as other agents featuring classical pharmacological or hormetic activity. Some examples of phytochemicals which are well specified as chemical entities, exhibit biological activities applicable in food and healthcare sector, and are commercially available include: Apigenin; Berberin; Capsaicin; β-Carotene; Chlorogenic acid; Coenzyme Q10; Colchicine; Curcumin; Epicatechin, Epigallocatechin gallate; Folic acid; Genistein; Glycyrrhetic acid; Lipoic acid; Lutein; Lycopene; Naringenin; Omega-3 fatty acids; Quercetin; Resveratrol; Rutin; Silimarin; β-Sitosterol; Stevioside; Sulforaphane; Stigmasterol; and Zeaxanthin.

Place of phytochemicals in biological diversity and among health related products

Organic acids (and their salts) appear to be the first individual chemicals of low molecular weight isolable from plant tissues in the pure state but their failed to make impact on medical practices of the time. Real breakthrough, described as emergence of pharmacognosy, came with isolation of organic base – morphine (Serturner 1805), from narcotic papaver juice (opium), soon followed by avalanche of other alkaloids, which marked commencement of such research fields as natural product chemistry and medicinal chemistry, greatly influencing development of pharmacology and organic chemistry [3,5,28]. Thus established link between plant biogenesis products and human physiology continues, despite of pressure from synthetic medicines, reflected by the fact that significant proportion of modern drugs come directly, or through some minor synthetic modifications, from the pool of secondary metabolites such as acetogenins, isoprenoids, alkaloids, flavonoids, etc., which are categorized from the point of view of therapeutic utility as: vitamins, antibiotics, anticancer agents, and cardiovascular, metabolic, CNS drugs, among others [4,28,29]. Medicinal chemistry is characterized by everlasting strive for new structures, in belief that molecular architecture can determine biological activity in terms of selectivity as well as efficacy. Chemical space concept, accommodating all possible molecules denoted as tree-dimensional atom linking structures serves well development of chemoinformatic methods for structure – activity relationship studies, but it is not particularly practical in search for new drugs, because of unimaginably vast number of objects to scan for desired properties [30]. Situation looks quite different in the biological world, with vast but finite number of species and organisms. Biological diversity of our planet is estimated to accommodate ca. 8.7 mln of species in all kingdoms of life (of which ca. 2.2 mln belongs to the marine environment) [31,32]. With an assumption that primary metabolism is largely shared at least within phyla, and that secondary metabolism can be redundant in lower taxonomic units, we can still expect to find around millions of compounds with new structures. A great virtue of chemical diversity generated by living organisms resides in their inherent biocompatibility, contrasting with majority of compounds delivered by organic synthesis. Our current knowledge of natural products structural diversity accumulated over ca. two centuries of meticulous organisms taxonomic identification, isolation and structure elucidation of their metabolites, and study of their biochemical dynamics. As a result, secondary metabolite databases, categorized as acetogenins, alkaloids, flavonoids, isoprenoids, phenolics, etc., run into thousands, with total in order of mere 200 000 structures of chemical individuals with reasonable record of physicochemical, spectral and biological activity data [32]. Traditional pharmacognosy, which relied to a large extent, on chemical methods for phytochemical group analysis, and often required such extensive efforts as the total synthesis for the ultimate proof of an isolated compound structure, could not cope with entire complexity of a plant biochemical dynamics. More often than not, plant material was characterized by the presence of single secondary metabolite, functioning as a chemical marker for purpose of analytical specification. Today, superb collection of very sensitive and selective combined analytical techniques exists, which enables extensive chemical fingerprinting of biological materials and study of complete metabolomes of chosen organisms [33,34]. Consequently, it became evident that a single plant metabolome can comprise even thousands of compounds, which can in principle influence human biochemical networks on cellular, tissue, organ and organismal levels. In fact, consumption of a plant composed diet (fruits, vegetables, spices, etc.) leads to interaction of plant metabolites with a host and its microbiome systems, in a highly complicated network with multiple ligands competing for multitude of macromolecular targets, with possible reciprocal regulatory effects. Every step of interaction between metabolomes of different biological species requires management and analysis of huge amount of data, far beyond the scope of classical pharmacology, concentrating on simplified two bodies (ligand and target) interaction models. New bioinformatic and chemoinformatic tools, modeling intermolecular energetics, macromolecular dynamics and ligand exchange as well as other transformations of biomolecules will ultimately help to formulate network pharmacology, based on deeper insight in regulatory biochemical processes underlying systems biology [3,8,35,36]. In view of frequently overlooked fact that entire drug armamentarium of contemporary medicine consist on little over ten thousand active substances in the low molecular weight category, it seems obvious that combined affluence of known secondary metabolites and compounds yet to be discovered from natural sources should be sufficient to satisfy most of the currently unmet medicinal needs. However, development of phytochemicals into new registered drugs, and all kinds of new health improving and health supporting preparations beyond restricted category of prescription drugs, will require supply of corresponding active substances in substantial amounts and in good chemical purity.

Examples of medicinally relevant activity from phenolic phytochemicals category

Going through collections of plant secondary metabolites it would be difficult to overlook the fact, that phenolics are not only exceptionally numerous, but also their structural features make them susceptible to many kind of intermolecular interactions, of various strength and character. Indeed, also test tube reactivity of phenols is known for exceptionally array of processes characterized as nucleophilic, electrophilic and free radical additions. Not surprisingly, this chemical pluripotency strongly influences pharmacological profiles of compounds containing one of more hydroxyl groups attached to an aromatic ring in their structures [37-39]. Phytochemical phenolic biogenesis involves either combination of two-carbon units (acetogenins) or shikimic acid pathway, with phenylalanine deamination step on the way. Phenylpropanoids, most often described as flavonoids, constitute the most prominent group of plant phenolics. At the beginning of XXth century flavonoids were studied mainly as plant pigments with some limited application in textile industry. In 1940-ies isoflavones of subterraneous clover were found to interfere with sheep breeding and their affinity to estrogen receptors become a topic of lasting studies [40]. Inhibition of protein kinase A activity by genistein was the next big news for soy isoflavones. Flavones, flavonols and catechins, as well as their precusors – chalcones, were recognized as modulators of intracellular signal transduction pathways, while all classes of flavonoids qualified as antioxidants and effective scavengers of reactive forms of oxygen and nitrogen, which are known to exert devastating influence on essentials biomacromolecules [13,14,41,42]. Poor bioavailability of flavonoids practically excluded them from drug development projects, but they are amply represented in dietary supplement products, in capacity of phytoestrogens, apoptosis promoters and growth factors regulators [14,16]. Flavonoid glycosides deserve special attention, for their increased metabolic stability, modulated pharmacokinetics and pharmacodynamics, in respect to parent aglycone [43-44]. Recently, whole new generation of antidiabetic drugs (glycoside mimetics “gliptins” – the sodium-glucose transport protein 2 inhibitors) evolved from the well-known phytochemical - phlorizin, which formally belongs to dihydrochalcone glycosides category [45]. As a result, certain revival of interest in flavonoids and their derivatives can be noticed. Since wider array of biological activity tests came into use, and more attention has been paid to bioavailability of flavonoids [38,46], some supplemented lists of their pharmacological activity appeared [38,47-48]. One example of entirely new type of biological activity has surfaced recently in connection with research on flavonol: fisetin, one of primary yellow plant pigments, which started period of valiant discoveries of S. Kostanecki and his group, the founders of flavone chemistry field, at the end of 19th century. Fisetin (but not its 5-deoxy congener – quercetin), is reported to be a cellular senescence inhibitor, an activity of great interest in perspective of possible influence on aging process [49,50]. Effective senescent cell elimination with fisetin, observed on a mouse model [49] operates by thus far unknown mechanism. It would be interesting to find out if some other flavonoids share this unique activity with obvious health related utility.

Perspectives concerning availability of flavonoids and other phytochemicals for development and commercialization

There is a convincing evidence that polyphenol-rich vegetable food, spices, and beverages, exert beneficial effects on human physiology [23,37-39,51,52]. The same applies to a better defined phytochemical category - flavonoids – more narrow, biogenetically uniform, and relatively easily available substances, traditionally obtainable by plant extracts separations [40-42]. While nutraceutical industry is happy with an analytical specification of plant raw materials, including fingerprinting with modern hyphenated separation and detection techniques, academic life sciences exhibit strong drive for study of phytochemicals as individual chemical entities, not as constituents of native biological matrix. Low molecular weight flavonoids (phenylpropanoids) are fairly simple compounds with a fifteen carbon atoms basic skeleton, for which many synthetic chemical methods are presently available [37,40,50]. Considering a scale of the future demand for phytochemicals as active ingredients, commensurate with nutraceutical and dietary supplements sector dynamics, it is clear that new, biotechnological processes of their manufacturing are needed, which would fit requirements of future bioeconomy. Synthetic biology and metabolic engineering can presently deliver great variety of chemicals, particularly known metabolites, by sequential application of genetic engineering, protein engineering, and pathway engineering to a selected organism, which culminates in turning its metabolism into a cell factory overproducing programmed product [53,54]. There are practically no technical limits to application of these new techniques for phytochemical manufacturing processes.

Conclusion

Natural products remain essential source of inspiration in drug discovery and also provide driving force for innovation in dynamic sector of functional food and beverages industry [3,14,55]. Current functional foods market seems to focus on condition-specified products (weight management, performance, stress, cognition, etc.), while avoiding health claims restricted to registered medicinal preparations. The prevention of "civilization diseases", including metabolic syndrome (cardiovascular ailments, dyslipidemia and diabetes), cancer and neurodegeneration, would be an excellent prime target for application of natural products, since substantial epidemiological evidence already exists, suggesting health beneficial effects of consumption phenolic-rich vegetable diets [37-39]. However, it is unlikely that such mission could be carried out under nutraceuticals umbrella term, for formal reasons listed in current literature [17,20,29,55]. It is clear that for such task a new definition of specialty ingredients of natural origin, based on their chemical specification, pharmacological activity and clinical validation, would be required, to define application regiments and assure their safety. Phytochemicals (incuding many secondary metabolites listed as nutraceuticals), thus far known as research materials in biochemistry, physiology and pharmacology, already became available on non-pharmaceutical healthcare product markets, with authorizations based on status of "old dietary ingredient" and/or "generally recognized as safe". Progress of academic research on natural products chemistry and biology, together with availability of its results in public domain through open science media, created not only new market trends but also new type of consumer awareness and acceptance. Apparently, there are many ways to exploit vast resources of natural products for betterment of human health and well-being, as demonstrated by achievements of contemporary pharmaceutical industry. Among new alleys of research, the one focusing on metabolome interactions (host, its microbiome and dietary plants), analyzed in terms of molecular networks structure and dynamics, seems to be the most promising [4,35,36,46,52]. It seems likely that among variety of phytochemicals currently studied according to best rules of metabolomics, systems biology and bioinformatics, these which are already on the market will strengthen their position, while many more will attain the level of safety and chemoprevention efficacy acceptance, allowing some form of their market authorization.

Conflict of Interest

The author declares no conflict of interest.

Bibliography

1. Duke JA., "Handbook of Biologically Active Phytochemicals and Their Activities". CRC Press, Boca Raton, FL, USA (1992).
2. Crozier A., *et al*. "Plant Secondary Metabolites Occurrence, Structure and Role in the Human Diet". Blackwell Publishing LTD. London (2006).
3. Rao V. "Phytochemicals – a global perspective of their role in nutrition and health" Intechopen.com Rijeka CR (2012).
4. Huang L. "Molecular Pharmacognosy". Springer, Dordrecht (2013).
5. Newman DJ., *et al*. "The influence of natural products upon drug discovery". *Natural Product Reports* 17 (2000): 215-234.
6. Newman DJ and Cragg GM. "Natural Products as Sources of New Drugs from 1981 to 2014". *Journal of Natural Products* 79.3 (2016): 629-661.

7. Kaneko K. "Life: an introduction to complex systems biology". Springer-Verlag, Berlin (2006).

8. Klipp E., *et al*. Systems biology: a textbook, 2nd Edition, Wiley-VCH Weinheim (2016).

9. Sporn M.B., *et al*. "Prevention of chemical cancerogenesis by vitamin A and its synthetic analogs". *Federation Proceedings* 35.6 (1976): 1332-1338.

10. Sporn MB and Liby KT. "Cancer chemoprevention: scientific promise, clinical uncertainty". *Nature Clinical Practice Oncology* 2.10 (2005): 518-528.

11. Greiner AK., *et al*. "Chemoprevention in gastrointestinal physiology and disease. Natural products and microbiome". *American Journal of Physiology Gastrointestinal Liver Physiology* 307.1 (2014): G1-G15.

12. Madrigal-Santillan E., *et al*., "The chemoprevention of chronic degenerative disease through dietary antioxidants: progress, promise and evidences". in: Oxidative Stress and Chronic Degenerative Diseases - A Role for Antioxidants, Intech Open Rijeka (2013): 155-185.

13. Ramawat KG and Mérillon JM. "Bioactive Molecules and Medicinal Plants". Springer Verlag Berlin (2008).

14. Prakash D and Sharma G. "Phytochemicals of nutraceutical importance". *CAB International Boston MA USA* (2014).

15. DeFelice SL., "The nutraceutical revolution: its impact on food industry R&D". *Trends in Food Science and Technology* 6 (1995): 59-61.

16. Dillard CJ and German JB., "Phytochemicals: nutraceuticals and human health". *Journal of the Science of Food and Agriculture* 80 (2000): 1844-1856.

17. Zeisel SH., "Regulation of nutraceuticals". *Science* 285 (1999): 185-186.

18. Augustin MA and Sanguansri L. "Challenges and solutions to incorporation of nutraceuticals in foods". *Annual Review of Food Science and Technology* 6 (2015): 463–477.

19. Schmitt J and Ferro A. "Nutraceuticals: is there good science behind the hype?". *British Journal of Clinical Pharmacology* 75 (2013): 585–587.

20. Aronson JK., "Defining 'nutraceuticals': neither nutritious nor pharmaceutical". *British Journal of Clinical Pharmacology* 83 (2017): 8–19.

21. Estruch R., *et al*. "Primary prevention of cardiovascular disease with a Mediterranean diet". *New England Journal of Medicine* 368 (2013): 1279–1290.

22. Williams RJ., *et al*. "Neuro-nutraceuticals: The path to brain health via nourishment is not so distant". *Neurochemistry International* 89 (2015): 1-6.

23. Loffredo L., *et al*. "Antioxidant and antiplatelet activity by polyphenol-rich nutrients: focus on extravirgin oil and cocoa". *British Journal of Clinical Pharmacology* 83 (2017): 96–102.

24. Borghi C and Cicero AFG. "Nutraceuticals with clinically detectable blood pressure lowering effect: a review of available randomized clinical trials and their meta-analyses". *British Journal of Clinical Pharmacology* 83 (2017): 163–171.

25. Holst B and Williamson G. "Nutrients and phytochemicals: from bioavailability to bioefficacy beyond antioxidants". *Current Opinion in Biotechnology* 19 (2008): 73-82.

26. Banach M., *et al*. "The role of nutraceuticals in statin intolerant patients". *Journal of the American College of Cardiology* 72.1 (2018): 96-118.

27. Barrios V., *et al*. "A nutraceutical approach (Armolipid Plus) to reduce total LDL cholesterol in individuals with mild to moderate dyslipidemia: review of the clinical evidence". *Atherosclerosis Supplements* 24 (2017): 1-15.

28. Sneader W., *et al*. Drug discovery. A history, John Wiley and Sons Ltd., Chichester UK (2005): 88-150.

29. Manach C., *et al*. "The complex links between dietary phytochemicals and human health deciphered by metabolomics". *Molecular Nutrition and Food Research* 53 (2009): 1303-1315.

30. Renner S., *et al*. "Bioactivity-guided mapping and navigation of chemical space". *Nature Chemical Biology* 5.8 (2009): 585-592.

31. Koch MA., *et al*. "Charting biologically relevant chemicals pace: a structural classifications of natural products (SCONP)". *Proceedings of the National Academy of Sciences* 102.48 (2005): 17272-17277.

32. Mora C., *et al* "How many species are there on earth and in the ocean?". *PLoS Biology* 9.8 (2011): e1001127.

33. Matoli L., *et al*. "A metabolite fingerprinting for the characterization of commercial botanical dietary supplements". *Metabolomics* 7 (2011): 437–445.

34. Shoyama Y. "Quality control of herbal medicines and related areas". InTech Rijeka CR (2011).

35. Csermely P., *et al*. "Structure and dynamics of molecular networks: a novel paradigm of drug discovery, a comprehensive review". *Pharmacology and Therapeutics* 138 (2013): 333-408.

36. Pevsner J. Bioinformatics and functional genomics, 3rd Ed., Wiley Blackwell Chichester UK 2015.

37. Quideau S., *et al*. "Plant Polyphenols: Chemical Properties, Biological Activities, and Synthesis". *Angewandte Chemie International Edition* 50.3 (2011): 586-621.

38. Del Rio D., *et al*. "Dietary (poly)phenolics in human health: structures, bioavailability, and evidence of protective effects against chronic diseases". *Antioxidants and Redox Signaling* 18 (2013): 1818–1892.

39. Shahidi F., Ambigaipalan P. "Phenolics and polyphenolics in foods, beverages and spices: antioxidant activity and health effects – a review". *Journal of Functional Foods* 18 (2015): 820-897.

40. Grynkiewicz G. "Plant isoflavones, their impact on life sciences, medicine and industry". *Frontiers in Natural Products Chemistry* 3 (2017): 283-356.

41. Panche AN., *et al*. "Flavonoids: an overview". *Journal of Nutritional Sciences* 5 (2016): 1-15.

42. Wang T., *et al*. "Bioactive flavonoids in medicinal plants: structure, activity and biological fate". *Asian Journal of Pharmaceutical Sciences* 13 (2018): 12-23.

43. Grynkiewicz G and Szeja W. "Synthetic glycosides and glycoconjugates of low molecular weight natural products". *Current pharmaceutical design* 22.12 (2016): 1592-1627.

44. Yang B., *et al*. "New insights on bioactivities and biosynthesis of flavonoid glycosides". *Trends in Food Science and Technology* 79 (2018): 116-124.

45. Aguillon AR., *et al*. "Synthetic strategies toward SGLT2 inhibitors". *Organic Process Research and Development* 22 (2018): 467-488.

46. Rodriguez-Mateos A., *et al*. "Bioavailability, bioactivity and impact on health of dietary flavonoids and related compounds: an update". *Archives of Toxicology* 88 (2014): 1803-1853.

47. Pan M-H., *et al*. "Anti-inflammatory activity of natural dietary flavonoids". *Food and Function* 1 (2010): 15-31.

48. Hoensch HP and Oertel R. "The value of flavonoids for the human nutrition: short review and perspectives". *Clinical Nutrition Experimental* 3 (2015): 8-14.

49. Yousefzadeh MJ., *et al*. "Fisetin is a senotherapeutic that extends health and lifespan". *EBioMedicine* 36 (2018): 18-28.

50. Grynkiewicz G and Demchuk OM. "New perspectives for fisetin". *Frontiers in Chemistry* 7 (2019): 697-706.

51. Boeing H., *et al*. "Critical review: vegetables and fruit in the prevention of chronic diseases". *European Journal of Nutrition* 51 (2012): 637-663.

52. Williamson G., *et al*. "The bioavailability, transport, and bioactivity of dietary flavonoids: a review from a historical perspective". *Comprehensive Reviews in Food Science and Food Safety* 17 (2018): 1054-1112.

53. Stephanopoulos G. "Synthetic biology and metabolic engineering". *ACS SyntheticBiology* 1 (2012): 514-525.

54. Trantas EA., *et al*. "When plants produce not enough or at all: metabolic engineering of flavonoids in microbial hosts". *Frontiers in Plant Sciences* 6.7 (2015): 1-16.

55. Bagchi D and Nair S. "Developing New Functional Food and Nutraceutical Products". Elsevier Amsterdam (2017).

Volume 4 Issue 1 January 2020