Bioactive Chromone Derivatives – Structural Diversity

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Abstract: Chromones (1-benzopyran-4-ones) and chromone derivatives are naturally occurring compounds ubiquitously found in the plant kingdom, and therefore present in representative amounts in a normal human diet. These phytochemicals possess a wide spectrum of biological activities – such as anti-inflammatory, antifungal, antimicrobial, antiviral, antitumour and anticancer – mainly due to their well-recognised antioxidant properties, which stem from their ability to neutralise active forms of oxygen and to cut off free radical processes.

Since oxidative stress is known to be the basis for numerous severe pathologies, from cardiovascular and neurodegenerative disorders to cancer, the development of effective antioxidant agents from natural origin (namely dietary constituents) has been the object of vigorous research in the last decade, in view of establishing novel chemopreventive strategies against such diseases which are nowadays the main cause of death worldwide. In fact, the chromone moiety is an important element of pharmacophores of many biologically active molecules displaying diverse medicinal applications.

These potential health benefits arising from the antioxidant activity of chromone derivatives are ruled by strict structure-activity/structure-property relationships, which, apart from determining their biological action, modulate their systemic distribution and bioavailability in sites of oxidation within the cell.

The present work aims at reviewing the main reported studies on the cytoprotective and anticancer activities of chromone derivatives, with particular emphasis on the effect of their structural features and conformational behaviour on activity, which is the basis of a tailored design of novel chromone-based antioxidants for chemopreventive and chemotherapeutic use.

Keywords: Chromones, chemopreventive, chemotherapeutic, anticancer, structure-activity relationships (SAR).

1. INTRODUCTION

Modern lifestyle and diet has led to an increased exposure to free radicals, which is the cause of a higher susceptibility to disease. In fact, these oxidative stress conditions – disruption of the homeostatic balance between free radical generation and the production of naturally occurring antioxidants (*e.g.* glutathione and regulatory enzymes such as superoxide dismutase, catalase and peroxidases) – are well-known to be directly linked to a number of disorders due to oxidative damage in numerous cell targets (DNA, lipids, proteins). This finally result in severe diseases such as liver toxicity, cardiovascular and neurodegenerative (*e.g.* Alzheimer and Parkinson´s) pathologies, and cancer (Scheme **1**). These disorders are largely preventable through changes in diet, lifestyle and environmental conditions [1]. Hence, controlling or restoring the homeostatic oxidative balance is of the utmost relevance in the medical field.

Antioxidant defence mechanisms, however, are species dependent and heavily influenced by nutrition, since important antioxidants, such as ascorbic acid and α-tocopherol, cannot be synthesised by humans and must therefore be obtained exogenously [2]. Consequently, research focused on new antioxidants has been steadily developing in the last decade within the dietary and pharmacological fields, as evidenced by the number of new antioxidant products targeted for both the food industry and the cosmetics market, as well as for medicinal applications. In fact, the most amazing and effective tools for assisting human oxidative defence and fight disease may be growing in our own backyard [1,3-15].

Phytochemicals are defined as chemicals produced by plants, mostly concentrated in fruits, vegetables, wine, tea and cocoa, which display significant antioxidant and chelating properties. They are not considered as essential nutrients (such as proteins, carbohydrates, fats, minerals or vitamins), but are recognised to possess health-promoting properties since they have been progressively associated to biochemical defence mechanisms against bacteria, fungi, viruses and damage to cell structures, especially DNA. The three major classes of plant chemicals have been identified as phenolic derivatives, terpenoids and alkaloids [16]. The phenolic constituents, which are secondary metabolites, are the largest group and comprise anthocyanins, anthochlors, benzofurans, chromones (1-benzopyran-4-ones, Fig. (**1**)), coumarins, flavones and isoflavones (Fig. (**2**)), flavonones and flavonols, lignans, phenolic acids (hydroxybenzoic and hydroxycinnamic) and ketones, phenylpropanoids, quinonoids, stilbenoids, tannins and xanthones [17]. These polyphenols also present a

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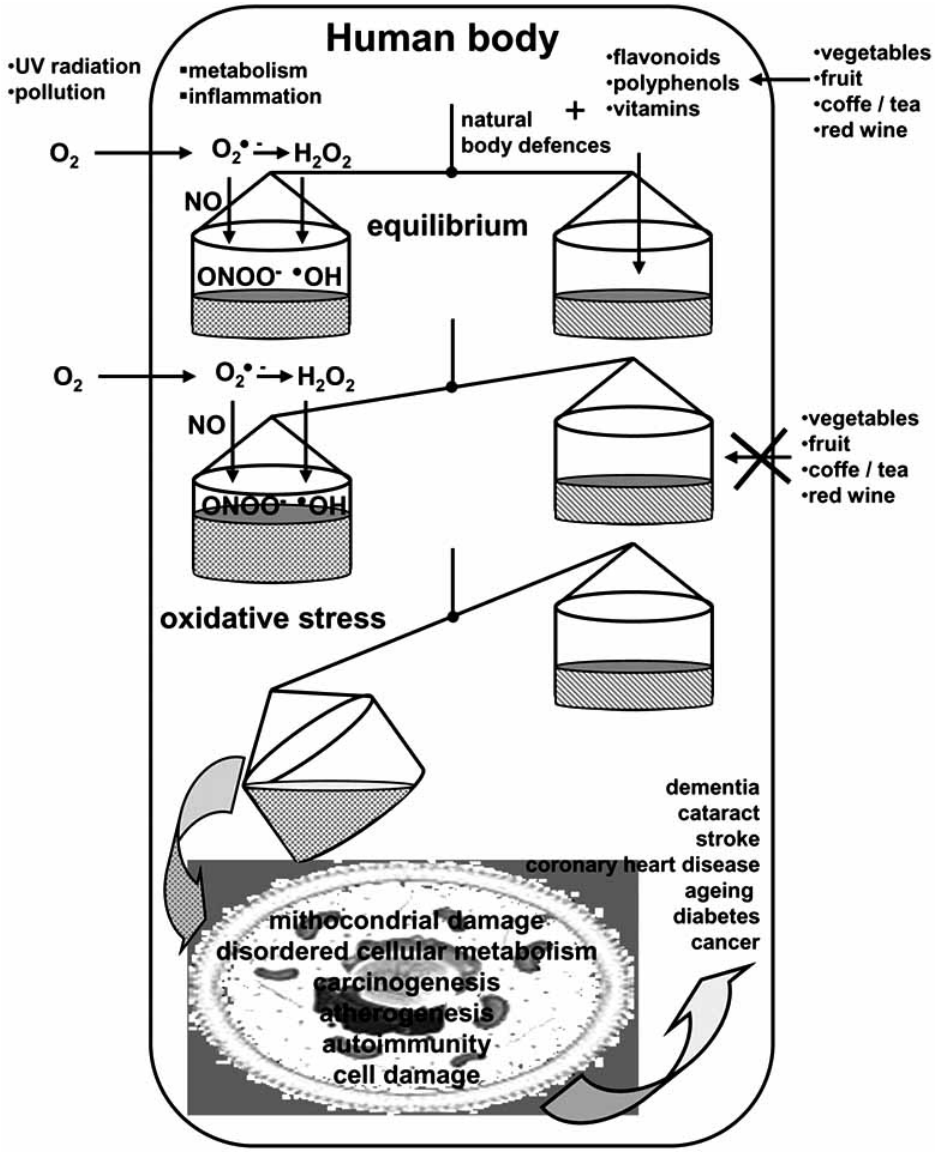


Scheme 1. Oxidative stress and its major biomedical consequences.

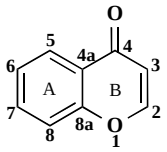


Fig. (1). Schematic representation of the chromone structure. (The atom numbering is included).

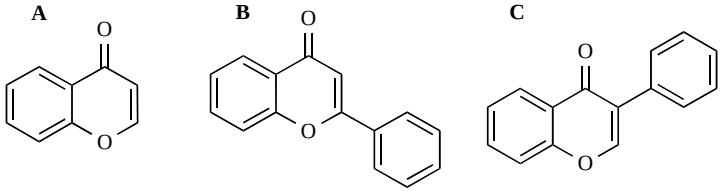


Fig. (2). Schematic representation of chromones (4*H*-benzopyran-4-one, (**A**)), flavones (2-phenyl-1,4-benzopyrone, (**B**)) and isoflavones (3-phenyl-1,4-benzopyrone, (**C**)).

distinctive ability to form inter-molecular interactions, either with each other (yielding dimeric species), or with other molecules such as biogenic polyamines (*e.g*. putrescine, spermidine or spermine) giving rise to a large variety of phenolic amides abundant in plants.

Mainly due to their well-recognised antioxidant properties – as a result of their marked tendency to transfer electrons, chelate ferrous ions, or scavenge reactive radicals – these naturally occurring heterocyclic compounds (comprising oxygen) are known to display pharmacologically relevant properties, namely antibacterial, antifungal, antiviral, anti-spasmolytic, anti-inflammatory, anti-HIV and anticancer [18-22]. In fact, protection against cancer as well as towards several age-related chronic diseases, provided by many common food constituents, has been observed in multiple epidemiological studies, and generally ascribed to non-nutritive dietary antioxidants such as chromone analogues. Consequentely, vigorous research (basic investigation and studies in both animal models and humans) has been carried out in order to understand and improve these potential health-beneficial agents. Prevention of cancer and cardiovascular distress through dietary intervention has therefore become an essential subject of research in the pharmacological and medicinal chemistry fields.

Although the use of plants for medicinal uses by indigenous people has been carried out for centuries, it was not before the 1980s and 1990s that the studies on phytochemicals entered the academic and industrial laboratories, aiming at their development for use as bioactive substances displaying specific health benefits – as preventive agents (nutraceuticals) or even as medicines – highlighting the importance of prevention, mainly when it became clear that therapy does not always succeed (*e.g*. due to drug resistance mechanisms) [23]. Therefore, strategies have been envisaged to modify dietary habits and complement the normal day-to-day diet with specific phytochemicals, as potential sources of antioxidants for phyto-pharmaceutical applications and functional food ingredients. Nevertheless, the complexity of the interactions between phytochemicals and other dietary components requires a thorough understanding of their mechanisms of action, which, in turn, relies on a detailed knowledge of the structural features and conformational preferences of these systems.

This manuscript is intended as a minireview comprising the main studies published in the last decade on the chemopreventive and chemotherapeutic properties of chromone derivatives, particularly against cancer, emphasizing the importance of structural and conformational factors on this biological activity. These structure-activity relationships (SAR´s) are the basis for the development of lead compounds aiming at a rational design of effective, chromone-based, preventive and/or anticancer agents.

2. CHEMOPREVENTION *VERSUS* CHEMOTHERAPY

It is widely established that exogenous antioxidants are needed for reducing the cumulative effects of oxidative damage over a life span, given the incomplete efficiency of our endogenous defence systems, their progressive breakdown with age and the existence of several factors responsible for ROS generation at the wrong time and place – cigarette smoke, air pollutants, UV radiation, fatty acid diet, inflammation, ischemia, etc. Thus, apart from the well established dietary antioxidants vitamins C, E, and A, and carotenoids, phytochemicals are gaining increasing importance as potential protective antioxidants.

There is presently compelling evidence that polyphenolic derivatives have an important role in chemoprevention and even chemotherapy against free radical mediated diseases such as cancer. They have been reported to interfere with the initiation, promotion and progression stages of the carcinogenesis process, highligting their importance as potential preventive and/or therapeutic natural agents. In fact, the intake of these compounds (*e.g.* chromone derivatives), namely through the diet, has been inversely related to the risk of developing various common neoplasms, such as lung, digestive tract and hormone-related cancers. Prostate cancer is a meaningful example: while hormone-refractory prostate cancer (HRPC) is a significant cause of death among men in the United States of America [24], individuals residing in Asia show a quite lower HRPC incidence when compared to caucasian males. In turn, asian men who move to and live in the USA, adopting a western lifestyle, have HRPC rates indistinguishable from caucasian males. These findings [25] suggest that asian diets contain ingredients that might protect against the development of this type of cancer, probably owing to a functional synergy between bioactive substances such as epigallocatechin gallate, genistein and quercetin.

Rossi and collaborators [26-29] have evaluated the relationship between flavonoid (2-phenyl-chromone, Fig. (**2**)) intake and the appearance of several types of human cancer, having established chemoprotective effects towards colorectal, pharyngeal, laryngeal, oral and ovarian cancer risk for this type of chromone-based compounds. Regarding prostate cancer, however, the results obtained by these researchers for this particular chromone analogue do not support a protective effect [30], which reflects selectivity, another relevant feature of the anticancer protective activity of this kind of systems. Additionally, dietary polyphenols were shown to possess beneficial cardiovascular effects [31,32].

These results add to the feasibility of attacking disease with an effective weapon – prevention – by developing a diet-based combinatorial approach, based on dietary polyphenols. Whereas chemotherapy is designed to destroy cancer after its appearance, chemoprevention aims at avoiding or at least delaying the onset of the neoplasm. The last decades of research in the field established prevention as the approach of choice in the struggle against cancer, as this pathology is much easier to prevent than to treat, and the former can be acomplished with a high degree of success through consumption of certain fruits and vegetables in the daily diet. Since cancer is a multifactorial disease, numerous pathways and molecular sites are to be considered as the targets of chemoprevention: apoptosis induction and downregulation of antiapoptotic proteins; suppression of growth factor expression; interference with intracellular signalling cascades; and downregulation of angiogenesis, among others. Phytochemicals, including chromone derivatives, have been determined as pharmacologically safe compounds able to modulate these specific molecular targets [33-35].

Chemoprevention is therefore generally accepted as the main benefit of natural and synthetic chromone constituents. Nonetheless, research on this type of systems, within a pharmacological and medicinal chemistry outlook, has progressively shown that they are also capable of exerting therapeutic effects and even of reversing chemoresistance [36,37], thus growing to be promising agents for use in novel chemotherapeutic strategies, mostly in combination with conventional therapies [38,39]. However, the mechanisms underlying their activity are not completely characterised, and many features still remain to be elucidated at a molecular level in order to clearly understand their mode of action and interference with cellular targets.

3. CHROMONES AS BIOACTIVE AGENTS

Chromones, a group of natural compounds comprising the 4H-benzopyran-4-one skeleton (Fig. (**1**)) present in several species of higher plants, are responsible for significant biological functions at nontoxic concentrations in living organisms. They display a marked antioxidant capacity [29, 40-49], through two main antioxidant pathways: 1) direct reaction with free radicals; 2) chelation of metal ions such as Fe(II) and Cu(II), involved in free radical-generating reactions (*e.g.* production of reactive oxygen species). Also, natural and dietary phenolic compounds (*e.g.* green tea polyphenols, soy isoflavones) have shown to be effective in suppressing invasiveness of cancer cells [50]. This is known to be a fundamental process in tumour progression and metastasis, intimately related to cell growth, cell adhesion, cell migration and proteolytic degradation of tissue barriers, which are mediated by specific intracellular signaling mechanisms. This inhibition of the invasive behaviour of cancer cells by dietary compounds can be considered as an adjuvant or combination anticancer therapy. Chromones and their structural analogues have therefore motivated a great interest within the medicinal chemistry field, the chromone moiety being the essential component of pharmacophores of a large number of bioactive molecules.

The term antioxidant has lately been redefined in a broader sense, to identify any substance that directly scavenges reactive oxygen species (ROS) (including deleterious cations such as Fe(II) or Cu(II)) or indirectly acts to upregulate antioxidant defences or inhibit ROS production. Chromones, in particular, are able to scavenge a wide range of ROS and can inhibit lipid peroxidation [42]. Although H-abstraction contributes most to this hydroxyl-radical-scavenging reactivity, electron transfer and the stability of the corresponding phenoxyl radicals resulting from H-abstraction also play an important role in this process. Free radical scavenging occurs by rapid donation of a hydrogen atom to the radical, and is therefore primarily attributed to the high reactivities of hydroxyl substituents that participate in this reaction:

$$C\text{-}OH + R^{\bullet} \rightarrow C\text{-}O^{\bullet} + RH$$

The radical scavenging activity of chromone derivatives obeys to strict conformational requirements, and is therefore determined by their molecular structure and substitution pattern (mainly OH substitution), which is reflected in the availability of phenolic hydrogens and in the degree of stabilisation of the resulting phenoxyl radical, either through H-bonding or by electron delocalisation [51,52].

Numerous studies are to be found, mostly in the last decade, on chromones and their analogues (*e.g.* flavonoids) as biologically active agents. Chromone derivatives, which are easily absorbed and metabolised, have been reported to display such significant activities as antimicrobial [53] and antifungal [47,54], anti-inflammatory [47,55-59], immunostimulatory [60], HIV-inhibitory [61,62], antimutagenic [63], antiproliferative [12,28,60,64-70], inductive of cell cycle arrest [44] and apoptosis [71-73], angiogenesis inhibition, and even reversive of multidrug resistance [12,39]. They were also found to act as neuroprotective [74] and anti-psychotic [75], and to exhibit antiplatelet aggregation effects [56,76], therapeutic efficacy against arthritis (in some cases higher than that of clinically used anti-inflammatory drugs such as Nimesulide [77]), and hypolipidemic activity [78], being also reported to function as selective sigma receptor ligands [79].

Different substitution patterns of the chromone skeleton can lead to considerable changes in their conformational behaviour and consequently their properties and function. Two-substituted chromones, in particular, exhibit a remarkable variety of biological activities, such as antiallergic or antineoplastic against several human cancer cells (*e.g.* leukaemia). Furthermore, chromones often disturb mitochondrial bioenergetics and enzymatic activities (*e.g.* succinate dehydrogenase, succinate cytochrome *c* reductase, and cytochrome *c* oxidase), in a dose-dependent way [80].

Sesquiterpene chromone derivatives (Fig. (**3**)) were reported to inhibit nitric oxide radical production [57,81]. In fact, NO is known to play a central role in inflammatory and immune reactions, excessive production leading to tissue damage (*e.g.* rheumatoid arthritis). Phenylethylchromones (with different hydroxyl and methoxyl substitutions [82]), in turn, have shown remarkable effects, namely at the central nervous system – 5-hydroxy-2-(2-phenylethyl)chromone, for instance, acts as a neuroprotector against glutamate-induced neurotoxicity [74,81]. Eugenitol (2,8-dimethyl-5,7-dihydroxy-chromone) and eugenitine (2,6-dimethyl-5-hydroxy-7-methoxy-chromone), which are important constituents of clove oil, were reported to behave as carcinogenesis inhibitors thanks to their remarkable antioxidant capacity. Nodulipreveneone, extracted from marine fungus, is a heterodimeric chromanone reported to act as a cancer chemopreventive agent *via* modulation of the xenobiotic metabolism [83].

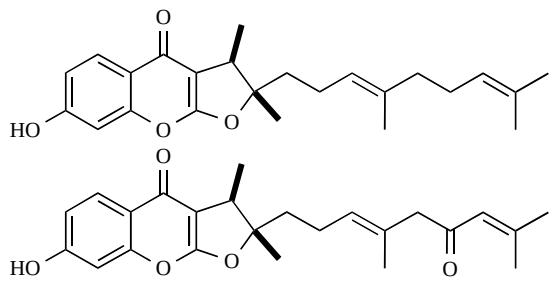


Fig. (3). Schematic representation of some sesquiterpene chromones (Adapted from [57]).

A new chromone derivative isolated from a marine fungus, 2-(hydroxymethyl)-8-methoxy-3-methyl-4H-chromen-4-one (chromanone A), showed to act as a promising inhibitor of several carcinogen metabolising enzymes [70]. Moreover, it displays a powerful and specific radical scavenging activity against hydroxyl radicals (more than peroxyl radicals), which is responsible for its protective effect towards oxidation-induced DNA damage in cells. Hence, chromanone A is a potential tumour anti-initiating agent.

Baicalein, a trihydroxylated flavonoid derivative, was found to be a potent and selective human lipoxygenase (LO) inhibitor [84], through direct binding of its catecholic moiety to the iron centre at the enzyme´s active site. This chromone derivative may therefore become a promising chemopreventive/chemotherapeutic agent, since lipoxygenase is implicated in pathologies such as asthma, immune disorders and several types of cancer.

Tangeretin (5,6,7,8,4´-pentamethoxyflavone) and nobiletin (5,6,7,8,3´,4´-hexamethoxy-flavone) (Fig. (**4**) (**A**) and (**B**)) are polymethoxylated flavonoids concentrated in the peel of citrus fruits, that are among the most effective polyphenols at inhibiting cancer cell growth both *in vitro* and *in vivo*, having demonstrated a particularly interesting activity [85-91]. In fact, for some cell lines (*e.g.* human breast MDA-MB-435 and MCF-7, and colon cancer HT-29) these compounds were verified to block cell cycle progression at phase G1 (60 to 95% inhibition for *ca.* 60 μM, already after 12 h of administration), but no apoptosis. This type of antitumour activity without inducing cell death (cytostatic activity) may be beneficial for clinical use, as it restricts proliferation in a manner less likely to affect normal, non-neoplastic tissues. In addition, its high level of methoxylation (5 or 6 methoxyl groups) is responsible for a significant hydrophobic character, which favours transport and cellular uptake. Moreover, no signs of toxicity (namely to the liver, kidney or pancreas) were found following several weeks of tangeretin or nobiletin consumption [92]. Furthermore, tangeretin was also verified to behave as antimetastatic [93] and brain protector [94].

Another polymethoxylated chromone analogue, zapotin (5,6,2´,6´-tetramethoxyflavone, Fig. (**4**) (**C**)), contained in the edible fruit *Casimiroa edulis*, was found to induce apoptosis in cultured human promyelocytic leukemia cells (HL-60 cells) [95]. In addition, this compound was verified to inhibit the enzyme ornithine decarboxylase, essential for the synthesis of biogenic polyamines (putrescine, spermidine and spermine) and therefore for cell growth and differentiation, in human bladder carcinoma cells. Also, it was determined to affect the nuclear factor-kappa B activity in human hepatocellular liver carcinoma cell lines. Accordingly, zapotin is presently the object of intense study aiming at its development as a potential cancer chemopreventive agent.

Lately, a novel class of chromones found in nature, styrylchromones (Fig. (**5**)), have been recognised as potent antioxidants with promising pharmacological properties. Indeed, these vinyl-analogues of flavones have shown protective activity against oxidation-induced hepatotoxicity [42,96], and antiproliferative effect towards several human carcinomas inducing cell death through G1 arrest and DNA fragmentation [97]. While the number and position of the hydroxyl groups in the A-ring is undoubtly relevant for the

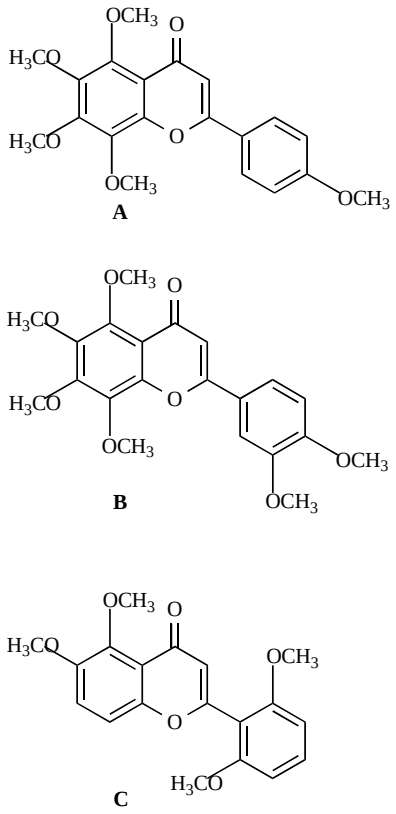


Fig. (4). Schematic representation of polymethoxylated chromone derivatives: tangeretin (**A**), nobiletin (**B**) and zapotin (**C**).

scavenging effect of these molecules, the styryl moiety was found to be responsible for an enhanced molecular stabilisation, therefore increasing the compound´s antiradical activity. A synthetic 2-styrylchromone, (3´-allyl-4´,5,7-trimethoxy-2-styrylchromone) was reported to disturb mithocondrial energetics in rats, leading to cell death through the induction of procaspases and a strong decrease of the available ATP [80]. A deleterious effect on the integrity of the mitochondrial membrane was also verified, leading to a respiratory activity depression.

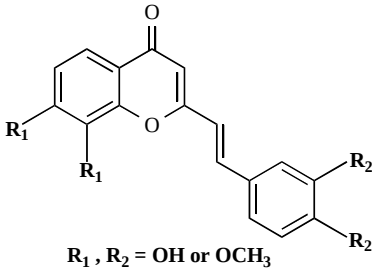


Fig. (5). Schematic representation of styrylchromones.

Phosphorus-containing chromones [98], in turn, constitute a novel group of compounds with interesting biological properties, such as antibacterial (particularly the 2-phosphorylated derivatives) and anticancer towards several tumour cell lines.

Glycosylated chromones (*O*- or *C*-glycosylated), either natural such as aloesin (extracted from various Aloe species) [58,59,99] (Fig. (**6**)) and baicalin (a baicalein *O*-glucuro-nide [100]), or synthetic such as hyperimone [101] (Fig. (**7**)), were shown to inhibit tyrosinase activity, improve insulin

sensitivity [102], exert hepatoprotective activity or even behave as cytotoxic agents [99]. This latter feature is of the utmost importance, since liver toxicity caused by chemicals and drugs has been long recognised as a serious toxicological problem, urging for the search of effective hepatoprotective agents obtained from natural sources. Also, due to the role of tyrosinase in melanin production, aloesin and its analogues are often used in cosmetics as inhibitors of hyperpigmentation induced by UV radiation [103]. Uncinoside, an *O*-glycosylated chromone, was showed to have antiviral activity against respiratory and parainfluenza virus [104] – both uncinoside A (5-hydroxy-2,6,8-trimethylchromone-7-*O*-β-D-glucopyranoside) and uncinoside B (5-acetoxyl-2,6,8-trimethyl-chromone-7-*O*-β-D-glucopyranoside). A *C*-glucosyl-chromone extracted from *Aloe barbadensis* (8-[*C*-β-d-[2-*O*-(*E*)-cinnamoyl]glucopyranosyl]-2-[(*R*)-2-hydroxypropyl]-7-methoxy-5-methylchromone) has been reported to have significant topical anti-inflammatory properties, comparable to those of hydrocortisone, without any reduction in thymus weight (as opposed to the classical hydrocortisone treatment) [105]. In fact, *A. Vera* has long been known to be a source of biologically relevant compounds with a wide range of health beneficial properties, namely glycosylated chromones [106].

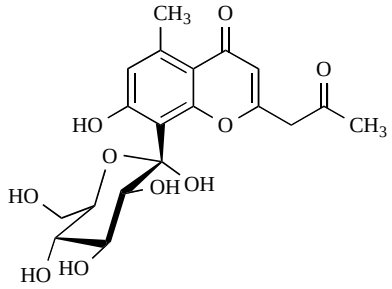
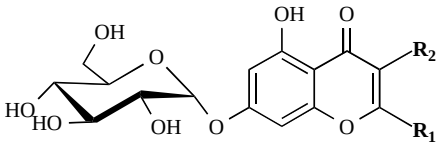


Fig. (6). Schematic representation of aloesin.



A $R_1 = CH(CH_3)_2$, $R_2 = H$
B $R_1 = H$, $R_2 = CH_3$

Fig. (7). Schematic representation of hyperimone A (**A**) and hyperimone B (**B**). (Adapted from [101]).

Furthermore, chromones and chromone derivatives are presently being used in adjuvant and/or combination therapy, since the efficiency of classical anticancer drugs has been verified to be improved by co-administration of these polyphenols. This has been observed for breast cancer chemotherapy with paclitaxel, for instance, cotreatment with chromone having led to a modulation of the drug´s transport and thus to a higher efficiency of chemotherapy in paclitaxel-resistant tumours [107].

In addition to these well known biological and medical properties of chromones and analogues, their complexes with metal ions have recently been recognised to be more effective than the ligands alone [19], which has opened new and promising routes in drug development. Although this is out of the scope of the present review, it should be mentioned that this kind of complexes have been successfully used in a range of pathologies such as diabetes mellitus, bacterial infections, certain types of cancer and neurodegenerative diseases (*e.g.* Huntington's disorder).

Apart from the recognised antiproliferative properties of chromone derivatives, clinical evidence indicates that cancer patients given phenolic antioxidants regularly exhibited higher tolerance and decreased chemotherapy side effects, and that they live longer and with a higher quality of life [108].

In the light of this broad biological activity, considerable attention has been devoted in the last two decades to the isolation of chromone derivatives from natural sources, and to research regarding their chemistry and biochemical function. Numerous chromone-based phytochemicals have been purified from plant extracts or synthetised *de novo*, their properties being determined by the different substitution pattern of the chromone skeleton. In recent years, due to increasing public interest in healthy lifestyles and disease prevention and treatment, dietary supplements and nutraceuticals containing high doses of this type of phenolic derivatives have been introduced to the market [109-111]. In addition, some have even entered clinical trials, namely the synthetic flavone flavopiridol (5,7-dihydroxy-8-(4-*N*-methyl-2-hydroxypyridyl)-6-chloroflavone hydrochloride, Fig. (**8**)), which is the first cyclin-dependent kinase inhibitor to be tested in humans, both in Phase II single-agent trials and Phase I combination trials (with paclitaxel and cisplatin, where a synergistic effect has been observed) [112-114]. In fact, cell cycle regulatory proteins such as cyclins and cyclin-dependent kinases (cdks) are potential molecular targets, since their functions are tightly controlled in normal cells but not in tumour cells. In fact, the preclinical studies on the synthetic flavopiridol evidence its capacity to induce programmed cell death, promote differentiation, inhibit angiogenic processes and modulate transcriptional events [113,114], as well as to enhance radiosensitivity in certain human cancers (by inhibiting repair of the radiation damage) [115].

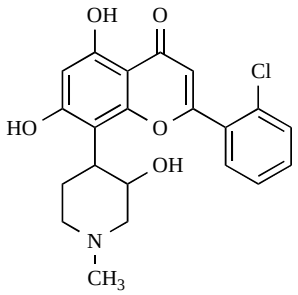


Fig. (8). Schematic representation of flavopiridol.

Accordingly, interpretation of this wide biological activity at a molecular level is urgent, aiming at the development of chromone-based compounds with promising pharmacological properties, either chemopreventive or chemotherapeutic against pathologies associated with oxidative stress, such as cancer and neurodegenerative disorders. This requires the establishment of accurate structure-activity relation-

ships, starting by the rational design of a lead compound to be structurally modified and screened as to both cytostatic/ cytotoxic and preventive capacities. This structure-based drug design relies on an accurate knowledge of the structural parameters and conformational preferences of the polyphenolic systems.

4. THE STRUCTURAL VARIABLE

Although the chromone moiety seems to be essential for most of the biological activity reported for this group of compounds, this has also been shown to be strictly dependent on other structural parameters, from the nature, number and position of the substituent groups to their relative orientation [116,117]. In fact, even a minor change in one of these factors can induce a considerable variation of the compound´s properties and therefore of its biological function. Conformational preferences such as flexibility, formation of hydrogen bonds – either intra- or intermolecular – and planar or skewed relative orientations of the substituent groups linked to the chromone skeleton determine the properties of the systems. The possibility of occurrence of hydrogen close contacts, for instance, can lead to a quite large stabilisation and therefore to a marked preference of a particular structure as opposed to other likely configurations (*e.g.* chromone-3-carboxylic acid *versus* chromone-2-carboxylic acid, Fig. (**9**) [N.F.L. Machado and M.P.M. Marques, unpublished results]).

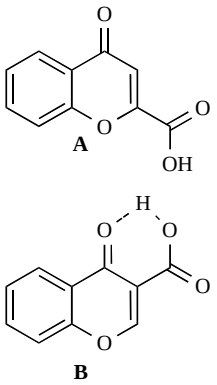
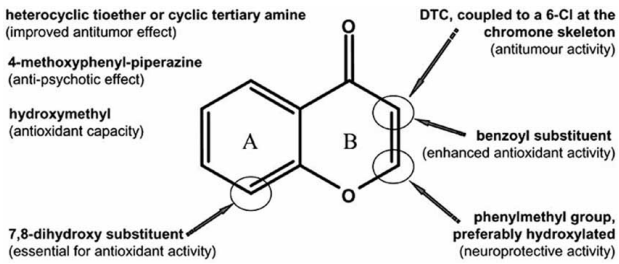


Fig. (9). Schematic representation of chromone-2-carboxylic acid (**A**) and chromone-3-carboxylic acid (**B**).

Additionally, the biological activity of these molecules is determined by their capacity to give rise to adducts with proteins, enzymes and biological receptors. Formation of these adducts *in vivo* is affected by the three-dimensional chromone structure and by the electronic distribution within the molecule – areas of highest electronegativity tend to appear at the 5-hydroxyl and 7-hydroxyl positions of the A-ring, as well as at the various hydroxylation sites on the B-ring (Fig. (**1**)).

In view of this preventive and therapeutic potential of chromone-derivatives, many researchers have therefore tried to elucidate possible structure-activity relationships that might lead to new drug discovery. Numerous studies are to be found in the literature reporting the synthesis and biologic screening of a series of such compounds, comprising different chemical entities added to a fixed chromone moiety. These structural modifications are then related to the measured activity and interpreted in the light of biochemical and pharmacological data obtained for the systems tested. Actually, while antioxidant activity relies on the presence of hydroxyl groups, other substituents were verified to affect this capacity, or to relate to distinct biological effects (Scheme **2**).



Scheme 2. Main structure-activity relationships (SAR´s) established for chromone derivatives. (DTC – dithiocarbamate).

Samee and coworkers [118] investigated the effect of structural modifications on the antioxidant activity of several chromones, having verified that it relies on the OH substitution in the aromatic A ring (mainly 8-OH substitution), and that the presence of a substituting benzoyl group in ring B (leading to an expanded conjugation system) significantly improved the radical scavenging capacity.

Huang and collaborators [44] described the synthesis and antitumour activities against various human solid tumours of a series of heterocyclic thioether chromone derivatives, determining the effect of a change in the heterocyclic moiety on their antiproliferative and cytotoxic capacities. One of the compounds tested (Fig. (**10**)) revealed a quite good activity against the mammary line MDA-MB-435S, with an IC_{50} equal to 17.2 μM, similar to that of 5-Fluorouracil (14.5 μM). In fact, numerous studies indicate that the presence of an heterocyclic thioether or a cyclic tertiary amine group will benefit the antitumour activity of chromone-based compounds [119-126].

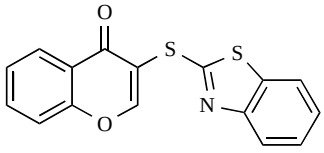


Fig. (10). Schematic representation of an heterocyclic thioether chromone derivative which showed a significant activity against the mammary human cancer line MDA-MB-435S. (Adapted from [44]).

The potential antipsychotic effect of several 2-[(4-benzyl-piperazinyl)methyl] chromones, namely their binding ability to sigma sites, was investigated [75]. It was verified that the introduction of a substituent in the chromone moiety, such as the replacement of methylenes by carbonyl groups, or of benzyl by aryl rings, led to a dramatic decrease in the affinity for these sites. In fact, among the most hopeful compounds which were found to act as potent and selective sigma ligands, the one containing a 4-methoxyphenyl substituted pyperazine moiety (Fig. (**11**)) [75] showed to be a promising candidate for the treatment of psychosis.

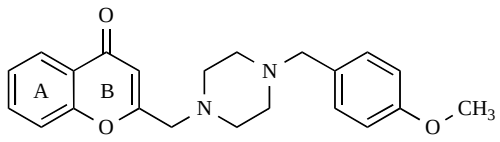


Fig. (11). Schematic representation of a novel 4-methoxyphenyl substituted 2-[(4-benzyl-piperazinyl)methyl chromone, shown to act as a promising selective sigma ligand. (Adapted from [75]).

Studies carried out on 2-(2-phenylethyl)chromones [74, 81,82] allowed to conclude that those derivatives comprising a 5-OH substituent and a phenylethyl moiety at position 2 (Fig. (**12**)) display a significant protective effect against glutamate-induced neurotoxicity, already for a 10 μM concentration. The hydroxylated phenylethyl derivative was verified to be more potent than the non-hydroxylated one, highlighting the relevance of the OH groups for antioxidant capacity. Moreover, activity showed to be strongly dependent on the structural preferences of the system, since a double bond in the phenylethyl arm (between C7´ and C8´, Fig. (**12**)) was found to inactivate these compounds as neuroprotectors. A high flexibility of this pendant group is therefore required for function, *i.e.*, for an efficient interaction with the specific receptors involved according to their conformational characteristics.

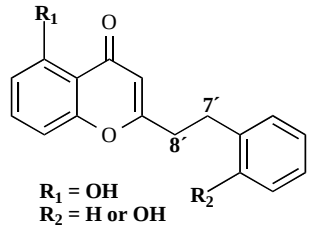


Fig. (12). Schematic representation of two 2-(2-phenylethyl) chromone derivatives displaying neuroprotective activity against glutamate-induced neurotoxicity. (Adapted from [74]).

In view of the well-known properties of dithiocarbamates (DTC) as antioxidants, fungicides, antivirals and even antiproliferative agents [127-130], several chromone analogues comprising diverse dithiocarbamate moieties were also synthesised. These were screened as to their *in vitro* growth-inhibiting capacity towards human tumour cells [43], some of them having shown significant dose-dependent effects and a broad-spectrum of activity. For these series of compounds, bearing the same DTC moiety at either positions 2 or 3 (Fig. (**13**)), it was verified that the antitumor activity was significantly improved by the introduction of a 6-Cl substituent in the chromone skeleton (as opposed to a chloride in the 7-position), while bulky DTC moieties were shown to be unfavourable. Two of these derivatives – 3-chloro-4-oxo-4H-chromen-2-yl)methyl piperidine-1-carbodithioate (Fig. (**13**) (A)) and 6-chloro-4-oxo-4H-chromen-3-yl)methyl piperidine-1-carbodithioate (Fig. (**13**) (B)) – evidenced a noteworthy dose-dependent effect against human mammary adenocarcinoma (MDA-MB-435S) and colon carcinoma (SW-480), through cell cycle arrest (at G2/M) and induction of apoptosis. The latter, in particular, was identified as the most promising candidate as a novel anticancer agent, since it exhibited a broad spectrum of activity, with IC_{50} values under 1.0 μM for all the cell lines tested (six distinct human carcinomas). The localisation of the DTC group was found to be determinant for activity, since this was drastically reduced when DTC was shifted from position 3 to 6 in the chromone rings. Also, the flexibility of the overall compound is a critical factor, since it rules the interplay between the chromone derivative and the biological target. In fact, removal of the methylene group linking the dithiocarbamate and the chromone B ring led to a marked activity decrease.

Despite the large number of experimental studies on the wide biological functions of chromone derivatives, there is still very little quantitative understanding about the relationships between their structure and conformational preferences, and the reported activity and potential beneficial effect on human health. Actually, the available data (Scheme **2**) still lacks a systematic analysis aiming at establishing reliable and useful structure-activity relationships (SAR´s and QSAR´s [131]).

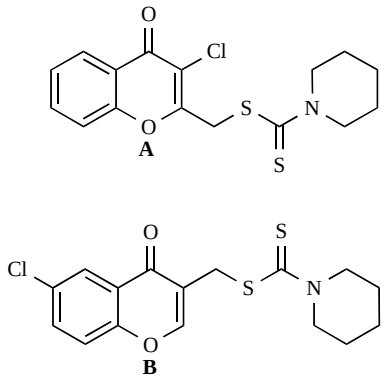


Fig. (13). Schematic representation of two dithiocarbamate substituted chromones with reported antitumour capacity: (3-chloro-4-oxo-4H-chromen-2-yl)methyl piperidine-1-carbodithioate (**A**) and 6-chloro-4-oxo-4H-chromen-3-yl)methyl piperidine-1-carbodithioate (**B**). (Adapted from [45]).

Theoretical calculations, at different levels (namely semi-empirical methods and quantum mechanical approaches such as Hartree-Foch and Density Functional Theory (DFT)), have been carried out for this kind of systems. These allowed to determine the main physical and electronic properties (descriptors) of relevance for antioxidant capacity, namely structural parameters and conformational preferences leading to an optimised biological activity. Several Physicochemical parameters have been determined for numerous phenolic compounds, in an attempt to elucidate the quantitative structure-activity relationships ruling their biological function [52,132-137]. This parameters include, among others, charge, number and relative position of the substituent hydroxyl groups, bond dissociation enthalpy, heat of formation, ionisation potential, electron affinity, electronegativity, electrophilic index, energies of the lowest unoccupied molecular orbital (LUMO) of the radical and of the highest occupied molecular orbital (HOMO) of the parent compound, and partition coefficient.

Such SAR and QSAR studies allowed to estimate the redox potentials and antioxidant activities and have been performed for naturally occurring chromones [138-142], while similar analysis on synthetic chromone derivatives have only recently appeared in the literature [118,138,139,

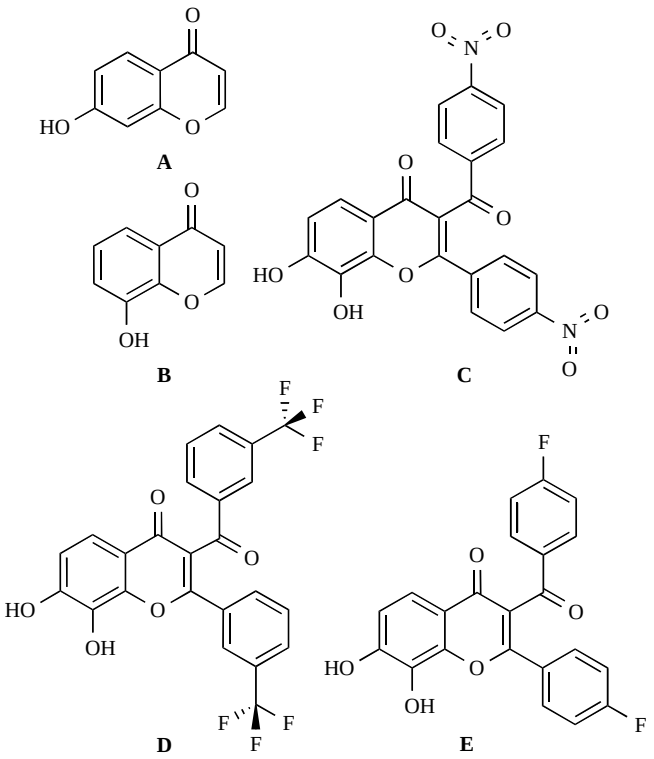


Fig. (14). Schematic representation of 7-hydroxy- (**A**) and 8-hydroxychromones (**B**), as well as 7,8-dihydroxychromones displaying high radical scavenging activity (**C** to **E**) (Adapted from [118]).

142-145]. Several dedicated algorithms have been developed for improving the correlation between predicted and experimental activities for this kind of systems. One of these approaches is the MOLMAP (Molecular Maps of Atom-level Properties), which encode local aspects of a chemical structure exclusively based on physicochemical properties, and can be interpreted as a fingerprint of the molecule´s reactivity [135].

A 3D-QSAR analysis was devoted to a series of synthetic hydroxychromones, for which the DPPH free radical scavenging activity was predicted by theoretical methods [145]. 7-hydroxy, 8-hydroxy and 7,8-dihydroxychromones (Fig. (**14**)) were evaluated, allowing to conclude that electronegative substituents on the benzoyl ring and electropositive groups on the phenyl ring play an important role for antioxidant activity, since they may help radical stabilisation throughout the chromone skeleton. In turn, high molecular weight and bulky substituents near position 5 and the carbonyl moiety are disfavoured, as the steric hindrance may disrupt the planarity between ring A and the carbonyl of the chromone nucleus, therefore affecting radical delocalisation [145].

Furthermore, QSAR models of the compound´s effects in biological systems – enzymatic structures, cells and organisms – have recently been attempted [145,146], in order to attain an accurate prediction of the chemopreventive and possible chemotherapeutic activity of the molecules under study. Although this is essencial for a rational design of new anti-inflammatory and anticancer chromone-based agents, it is not a straightforward task, since this type of compounds operate through a diverse array of antioxidant and non-antioxidant mechanisms.

The SAR-type studies carried out to this date on chromone derivatives allowed to identify specific structural components as requisites for radical scavenging, chelation and antioxidant activity. In fact, this was found to be mainly governed by the number, pK_a values and arrangement of the hydroxyl groups in the chromone ring system, as expected, since these are the groups responsible for the molecule´s reductive capacity through the formation of a stable radical [51,52,147,148]. Hence, a good correlation has been obtained between antioxidant and radical scavenging capacities and the hydroxyl bond strength, electron-donating ability (ionisation potential estimated by the HOMO energy), enthalpy of single electron transfer and spin distribution of the phenoxyl radicals after H-abstraction [52,138]. A double bond and a carbonyl function in the oxygen-containing heterocycle were verified to enhance activity by affording a more stable chromone radical through conjugation and electron delocalisation [147]. In turn, a decrease in the radical scavenging activity was detected upon methylation, mainly when it occurred at the B-ring [51,147,149]. Apart from these key factors, the lipophilic *vs* hydrophilic character is of the utmost importance in order to ensure both an efficient transport and a high bioavailability [147]. In this regard, the presence of a certain number of hydrophobic moieties has been recognised as beneficial, within a tight equilibrium between hydrophobic and hydrophilic groups. Methoxy groups, for instance (*e.g.* in tangeretin and nobiletin, Fig. (**4**)), increase lipophilicity and membrane partitioning, although they introduce unfavorable steric effects [46]. In fact, polymethoxylated chromones and flavones display a significantly low polarity and assume planar structures, which influences their permeabilities to biological membranes, metabolic fates and receptor-binding features.

These properties, in turn, play critical roles in the molecules' mode of action.

The presence or absence of an unsaturated 2–3 bond (Fig. (**1**)) in conjugation with a 4-oxo function are also relevant factors for activity. Most of the reported studies support that chromones lacking one or both of these features are less potent antioxidants than those with both elements. In fact, 2–3 unsaturation and a 4-carbonyl group have been correlated to a higher antioxidant capacity and to lower IC_{50} values in microssomal systems as compared to similar compounds with a saturated heterocycle. In summary, antioxidant potency appears to be enhanced by the presence of both 3-OH and 5-OH groups, in combination with a 2–3 double bond and a 4-carbonyl function, which are structural features that favour the phenoxyl radical stability [52].

7-hydroxychromones, in particular, are known to have a specially high antioxidant activity. Additionally, the relative position of the hydroxyl substituents and the interactions they can establish seem to be more important than the number of these groups. In fact, it was long verified that radical scavenging and metal chelating abilities (*e.g.* towards iron and cooper) require the presence of at least two vicinal OH´s [42], in a catechol-like arrangement (in fact catechol (1,2-hydroxybenzene) is a potent scavenger whereas phenol (hydroxybenzene) is not).

5. CONCLUSIONS AND FUTURE TRENDS

A regular intake of antioxidant compounds present in food – such as chromones and flavonoids – has long been recognised to be an important health-protecting factor. Accordingly, prevention of cancer through dietary intervention, as opposed to therapy after cancer growth, has been the object of increasing research in the last few years.

Two decades of SAR studies have allowed a basic understanding of the absorption, pharmacokinetics, and metabolism of chromone-derived compounds as a function of their structural and conformational preferences. Furthermore, metabolic changes, which include hydroxylation, *O*-methylation, cleavage of the heterocycle, deglycosylation, and scission of polymeric species into monomeric units, can not be disregarded, since activity can be either lost or enhanced upon metabolisation.

However, despite the unquestionable potential of this family of polyphenolic compounds as health-beneficial agents, supporting a positive role in human nutrition and disease prevention, additional and careful studies are crucial, namely focusing on their possible prooxidant role in the presence of some divalent ions (*e.g.* Cu(II)). In fact, reports of *in vitro* cytotoxicity, mutagenicity and proapoptotic effect related to some chromone derivatives raise obvious concerns, since many of these compounds are nowadays marketed as nutraceuticals (*e.g.* concentrated extracts of propolis, pine bark, green tea leaves, soy isoflavones and grape seeds). This prooxidant activity is thought to be closely related to the total number of hydroxyl groups.

Thus, some of the structural characteristics that optimise antioxidant capacity may also intensify oxidative stress and consequent damage to both functional and structural cellular molecules. Nevertheless, features favouring radical stability and therefore antioxidant activity (such as 3-OH and 5-OH, or 2–3 insaturation) may modulate these possible adverse oxidative effects. Moreover, glycosylation and methylation of OH groups attenuate the prooxidant behaviour of chromones-based compounds. In addition, while the presence of divalent iron or copper may accelerate prooxidant effects *in vivo*, chelation of these ions by the chromone analogues may theoretically revert this process. Besides, copper-initiated prooxidant reactions may not be significant *in vivo*, where the copper ion is largely sequestered, except maybe when certain metal overload diseases occur.

In addition to the structural and physico-chemical features of this type of phytochemicals, their absorption, pharmacokinetics, biotransformation and relative activities of the corresponding metabolites are critical determinants of their biological effects in organisms. Therefore, further investigation is justified in order to elucidate these factors and extend structure-activity relationships to preventive and therapeutic nutritional strategies. In due course, this line of study should lead to dietary recommendations regarding fruits, vegetables and other plant foods in the light of their health benefits, mainly targeting the aging population and individuals with an increased risk of cardiovascular distress, severe inflammatory conditions or cancer. Ultimately, the design of novel polyphenol-based chemopreventive and/or chemotherapeutic agents against oxidation-induced disorders is envisaged, with an emphasis on the development of new targeted therapeutics aimed at inducing cytostatic (rather than cytotoxic) effects.

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REFERENCES

[1] Riboli, E., Norat, T. Epidemiologic evidence of the protective effect of fruit and vegetables on cancer risk. *Am. J. Clin. Nutr.*, **2003**, *78*, 559S-569S.

[2] Benzie, I.F.F. Evolution of antioxidant defence mechanisms. *Eur. J. Nutr.*, **2000**, *39*, 53-61.

[3] Bravo, L. Polyphenols: chemistry, dietary sources, metabolism, and nutritional significance. *Nutr. Rev.*, **1998**, *56*, 317-333.

[4] Fresco, P., Borges, F., Diniz, C., Marques, M.P.M. New insights on the anticancer properties of dietary polyphenols. *Med. Res. Rev.*, **2006**, *26*(6), 747-766.

[5] Fresco, P., Borges, F., Marques, M.P.M., Diniz, C. The anticancer properties of dietary polyphenols and its relation with apoptosis. *Curr. Pharm. Des.*, **2010**, *16*, 114-134.

[6] Gomes, C.A., Girao da Cruz, T., Andrade, J.L., Milhazes, N., Borges, F., Marques, M.P.M. Anticancer activity of phenolic acids of natural or synthetic origin: a structure-activity study. *J. Med. Chem.*, **2003**, *46*, 5395-5401.

[7] Graf, B.A., Milbury, P.E., Blumberg, J.B. Flavonols, flavones, flavonones and human health: epidemiological evidence. *J. Med. Food*, **2005**, *8*, 281-290.

[8] Heijnen, C.G.M., Haenen, G.R.M.M., van Acker, F.A.A., van der Vijgh, W.J.F., Blast, A. Flavonoids as peroxynitrite scavengers: the role of the hydroxyl groups. *Toxicol. In Vitro*, **2001**, *15*, 3-6.

[9] Key, T.J., Schatzkin A., Willett, W.C., Allen, N.E., Spencer, E.A., Travis, R.C. Diet, nutrition and the prevention of cancer. *Public Health Nutr.*, **2004**, *7*, 187-200.

[10] Mandalari, G., Tomaino, A., Arcoraci, T., Martorana, M., Turco, V.L., Cacciola, F., Rich, G.T., Bisignano, C., Saija, A., Dugo, P., Cross, K.L., Parker, M. L., Waldron, K.W., Wickham, M. S. J.

Characterization of polyphenols, lipids and dietary fibre from almond skins (*Amygdalus communis* L.). *J. Food Compost. Anal.*, **2010**, *23*(2), 166-174.

[11] Pietta, P.G. Flavonoids as antioxidants. *J. Nat. Prod.*, **2000**, *63*, 1035-1042.

[12] Ren, W., Qiao, Z., Wang, H., Zhu, L., Zhang, L. Flavonoids: promising anticancer agents. *Med. Res. Rev.*, **2003**, *23*(4), 519-534.

[13] Surh, Y.J. Cancer chemoprevention with dietary phytochemicals. *Nat. Rev. Cancer*, **2003**, *3*, 768-780.

[14] Swinburn, B. Prevention of cancer. A colossal achievement, with much more to do. *Public Health Nutr.*, **2009**, *12*, 877-878.

[15] Veer, P., Jansen, M.C.J.F., Klerk, M., Kok, F.J. Fruits and vegetables in the prevention of cancer and cardiovascular disease. *Public Health Nutr.*, **1999**, *3*, 103-107.

[16] Harborne, J.B. Classes and functions of secondary products from plants. *In Chemicals from Plants – Perspectives on Plant Secondary Products*, Walton J.N., Brown D.E., Eds.; Imperial College Press: London, **1999**.

[17] Haslam, E. *Practical Polyphenolics*: *From Structure to Molecular Recognition and Physiological Action*, Cambridge University Press: Cambridge, **1998**.

[18] Bennardi, D.O., Romanelli, G.P., Jios, J.L., Autino, J.C., Baronetti, G.T., Thomas, H.J. Synthesis of substituted flavones and chromones using a Well-Dawson heteropoly acid as catalyst. *ARKIVOC*, **2008**, (vol. xi), 123-130.

[19] Grazul, M., Budzisz, E. Biological activity of metal ion complexes of chromones, coumarins and flavones. *Coord. Chem. Rev.*, **2009**, *253*, 2588-2598.

[20] Li, Y., Fang H., Xu, W. Recent advance in the research of flavonoids as anticancer agents. *Mini Rev. Med. Chem.*, **2007**, *7*, 663-678.

[21] Prasad, K.N., Xie, H., Hao, J., Yang, B., Qiu, S., Wei, X., Chen, F., Jiang, Y. Antioxidant and anticancer activities of 8-hydroxypsoralen isolated from wampee [Clausena lansium (Lour.) Skeels] peel. *Food Chem.*, **2010**, *118*, 62-66.

[22] Recanatini, M., Bisi, A., Cavalli, A., Belluti, F., Gobbi, S., Rampa, A., Valenti, P., Palzer, M., Palusczak, A., Hartmann, R.W. A new class of nonsteroidal aromatase inhibitors: design and synthesis of chromone and xanthone derivatives and inhibition of the P450 enzymes aromatase and 17α-hydroxylase/c17,20-lyase. *J. Med. Chem.*, **2001**, *44*, 672-680.

[23] Dillard C.J., German, J.B. Phytochemicals: nutraceuticals and human health. *J. Sci. Food Agric.*, **2003**, *80*, 1744-1756.

[24] Siddiqui, I.A., Saleem, M., Adhami, V.M., Asim M., Mukhtar, H. Tea beverage in chemoprevention and chemotherapy of prostate cancer. *Acta Pharmacol. Sin.*, **2007**, *28*, 1392-1408.

[25] Hsieh, T.C., Wu, J.M. Targeting CWR22Rv1 prostate cancer cell proliferation and gene expression by combinations of the phytochemicals EGCG, genistein and quercetin. *Anticancer Res.*, **2009**, *29*(10), 4025-4032.

[26] Garavello, W., Rossi, M., McLaughlin, J.K., Bosetti, C., Negri, E., Lagiou, P., Talamini, R., Franceschi, S., Parpinel, M., Dal Maso L., La Vecchia C. Flavonoids and laryngeal cancer risk in Italy. *Ann. Oncol.*, **2007**, *18*, 1104-1109.

[27] Rossi, M., Garavello, W., Talamini, R., Negri, E., Bosetti, C., Dal Maso, L., Lagiou, P., Tavani, A., Polesel, J., Barzan, L., Ramazzotti, V., Franceschi S., La Vecchia, C. Flavonoids and the risk of oral and pharyngeal cancer: a case-control study from Italy. *Cancer Epidemiol. Biomarkers Prev.*, **2007**, *16*, 1621-1625.

[28] Rossi, M., Negri, E., Lagiou, P., Talamini, R., Dal Maso, L., Montella, M., Franceschi, S., La Vecchia, C. Flavonoids and ovarian cancer risk: a case-control study in Italy. *Int. J. Cancer*, **2008**, *123*, 895-898.

[29] Rossi, M., Negri, E., Talamini, R., Bosetti, C., Parpinel, M., Gnagnarella, P., Franceschi, S., Dal Maso, L., Montella, M., Giacosa A., La Vecchia, C. Flavonoids and colorectal cancer in Italy. *Cancer Epidemiol .Biomarkers Prev.*, **2006**, *15*, 1555-1558.

[30] Bosetti, C., Bravi, F., Talamini, R., Parpinel, M., Gnagnarella, P., Negri, E., Montella, M., Lagiou, P., Franceschi S., La Vecchia, C. flavonoids and prostate cancer: a study in Italy. *Nutr. Cancer*, **2006**, *56*, 123-127.

[31] Mink, P.J., Scrafford, C.G., Barraj, L.M., Harnack, L., Hong, C.P., Nettleton J.A., Jacobs, D.R. Flavonoid intake and cardiovascular disease mortality: a prospective study in postmenopausal women. *Am. J. Clin. Nutr.*, **2007**, *85*, 895-909.

[32] Ostertag, L.M., O'Kennedy, N., Kroon, P.A., Duthie G.G., De Roos, B. Impact of dietary polyphenols on human platelet function – A critical review of controlled dietary intervention studies. *Mol. Nutr. Food Res.*, **2010**, *54*, 60-81.

[33] Manson, M.M. Inhibition of Survival Signaling by Dietary Polyphenols and Indole-3-carbinol. *Eur. J. Cancer*, **2005**, *41*, 1842-1853.

[34] Manson, M.M. Cancer prevention – the potential for diet to modulate molecular signaling. *Trends Mol. Med.*, **2003**, *9*, 11-18.

[35] Sarkar F.H., Li, Y.W. Cell signaling pathways altered by natural chemopreventive agents. *Mutat. Res.*, **2004**, *555*, 53-64.

[36] Aggarwal, B.B., Takada, Y., Oommen, O.V. From chemoprevention to chemotherapy: common targets and common goals. *Exp. Opin. Invest. Drugs*, **2004**, *13*, 1327-1338.

[37] Ramos, S. Cancer chemoprevention and chemotherapy: Dietary polyphenols and signalling pathways. *Mol. Nutr. Food Res.*, **2008**, *52*, 507-526.

[38] Sarkar, F.H., Li, Y. Targeting multiple signal pathways by chemopreventive agents for cancer prevention and therapy. *Acta Pharmacol. Sin.*, **2007**, *28*, 1305-1315.

[39] Wu, C.P., Calgano, S.B., Hladky, S.B., Ambudkar S.V., Barrand, M.A. Modulatory effects of plant phenols on human multi-drug resistance proteins 1, 4 and 5 (ABCC1, 4 and 5). *FEBS J.*, **2005**, *272*, 4725-4740.

[40] Chemler, J.A., Yan, Y., Leonard E., Koffas, M.A.G. Combinatorial mutasynthesis of flavonoid analogues from acrylic acids in microorganisms. *Org. Lett.*, **2007**, *9*(10), 1855-1858.

[41] Forghieri, M., Laggner, C., Paoli, P., Langer, T., Manao G., Camici C., Bondioli L., Fabio P., Costantino L. Synthesis, activity and molecular modeling of a new series of chromones as low molecular weight protein tyrosine phosphatase inhibitors. *Bioorg. Med. Chem.*, **2009**, *17*, 2658-2672.

[42] Gomes, A., Neuwirth, O., Freitas, M., Couto, D., Ribeiro, D., Figueiredo, A.G.P.R., Silva, A.M.S., Seixas, R.S.G.R., Pinto, D.C.G.A. Synthesis and antioxidant properties of new chromone derivatives. *Bioorg. Med. Chem.*, **2009**, *17*, 7218-7226.

[43] Huang, W., Ding, Y., Miao, Y., Liu, M., Li, Y., Yang, G. Synthesis and antitumor activity of novel dithiocarbamate substituted chromones. *Eur. J. Med. Chem.*, **2009**, *44*, 3687-3696.

[44] Huang, W., Liu, M., Li, Y., Tan, Y., Yang, G. Design, syntheses, and antitumor activity of novel chromone and aurone derivatives. *Bioorg. Med. Chem.*, **2007**, *15*, 5191-5197.

[45] Khan, K.M., Ambreen, M., Hussain S., Perveen S., Choudhari, M.I. Schiff bases of 3-formylchromone as thymidine phosphorylase inhibitors. *Bioorg. Med. Chem.*, **2009**, *17*, 2983-2988.

[46] Kuroda, M., Uchida, S., Watanabe K., Mimaki Y. Chromones from the tubes of *Eranthis ciclica* and their antioxidant activity. *Phytochemistry*, **2009**, *70*, 288-293.

[47] Rode, M., Gupta, R.C., Karale B.K., Rindhe, S.S. Synthesis and characterization of some substituted chromones as an anti-infective and antioxidant agents. *J. Heterocycl. Chem.*, **2008**, *45*, 1597-1602.

[48] Tang, H.A., Wang, X.F., Yang, S., Wang, L.F. Synthesis, characterization, and biological activities of Pt(II) and Pd(II) complexes with 2 ',3 ',4 ',5,7-pentahydroxy flavone. *Rare Metals*, **2004**, *23*, 38-42.

[49] Wang, Q., Yang, Z., Qi G., Qin D. Synthesis, crystal structure, antioxidant activities and DNA-binding studies of the Ln(III) complexes with 7-methoxychromone-3-carbaldehyde-(4´-hydroxy) benzoyl hydrazone. *Eur. J. Med. Chem.*, **2009**, *44*, 2425-2433.

[50] Silva D. Suppression of cancer invasiveness by dietary compounds. *Mini Rev. Med. Chem.*, **2008**, *8*, 677-688.

[51] Cao, G., Sofic, E., Prior, R. L. Antioxidant and prooxidant behavior of flavonoids: structure-activity relationsihps. *Free Radic. Biol. Med.*, **1997**, *22*, 749-760.

[52] Lien, E.S., Ren, S., Bui, H.H., Wang, R. Quantitative structure-activity relationship analysis of phenolic antioxidants. *Free Radic. Biol. Med.*, **1999**, *26*, 285-294.

[53] Deng, Y., Lee, J.P., Tianasoa-Ramamonjy, M., Snyder, J.K., Des Etages, S.A., Kanada, D., Snyder M.P., Turner, C.J. New antimicrobial flavanones from *Physena madagascariensis*. *J. Nat. Prod.*, **2000**, *63*, 1082-1089.

[54] Ma, W.G., Fuzzati, N., Lu, S.L., Gu S., Hostettmann, K. Further chromones from *Eriosema tuberosum*. *Phytochemistry*, **1996**, *43*, 1339-1343.

[55] Fujimoto, H., Nozawa, M., Okuyama E., Ishibashi, M. Five new chromones possessing monoamine oxidase inhibitory activity from an ascomycete, *Chaetomium quadrangulatum. Chem. Pharm. Bull.*, **2002**, *50*, 330-336.

[56] Mazzei, M., Sottofattori, E., Dondero, R., Ibrahim, M., Melloni E., Michetti, M. *N,N*-Dialkylaminosubstituted chromones and isoxazoles as potential anti-inflammatory agents. *Il Farmaco*, **1999**, *54*, 452-460.

[57] Motai T., Kitanaka, S. Sesquiterpene chromones from *Ferula fukanensis* and their nitric oxide production inhibitory effects. *J. Nat. Prod.*, **2005**, *68*, 1732-1735.

[58] Park, M., Kwon, H., Sung, M. Intestinal absorption of aloin, aloe-emodin, and aloesin; A comparative study using two *in vitro* absorption models. *Nutr. Res. Pract.*, **2009**, *3*, 9-14.

[59] Piao, L.Z., Park H.R., Park, Y.K., Lee, S.K., Park J.H., Park, M.K. Mushroom tyrosinase inhibition activity of some chromones. *Chem. Pharm. Bull.*, **2002**, *50*, 309-311.

[60] Gamal-Eldeen, A.M., Djemgou, P.C., Tchuendem, M., Ngadjui, B.T., Tane P., Toshifumi, H. Anti-cancer and immunostimulatory activity of chromones and other constituents from Cassia petersiana. *Z. Naturforsch C*, **2007**, *62*, 331-338.

[61] Park, J.H., Lee, S.U., Kim, S.H., Shin, S.Y., Lee, J.Y., Shin, C.G., Yoo K.H., Lee, Y.S. Chromone and chromanone derivatives as strand transfer inhibitors of HIV-1 integrase. *Arch. Pharmacol. Res.*, **2008**, *31*, 1-5.

[62] Yu, D., Chen, C.H., Brossi A., Lee, K.H. Anti-AIDS agents 60. Substituted 3'*R*,4'*R*-Di-*O*-(-)-camphanoyl-2',2'-dimethyldihydropyrano[2,3-*f*]chromone (DCP) analogues as potent anti-HIV agents. *J. Med. Chem.*, **2004**, *47*, 4072-4082.

[63] Mitscher, L.A., Telikepalli, H., McGhee E., Shankel, D.M. Natural antimutagenic agents. *Mutat. Res.*, **1996**, *350*, 143-152.

[64] Conrad, J., Forster-Fromme, B., Constantin, M.A., Ondrus, V., Mika, S., Mert-Balci, F., Klaiber, I., Pfannstiel, J., Moller, W., Rosner, H., Forster-Fromme K., Beifuss, U. Flavonoid glucuronides and a chromone from the aquatic macrophyte *Stratiotes aloides*. *J. Nat. Prod.*, **2009**, *72*, 835-840.

[65] Ferrari, F., Delle Monache, F., Suarez, A. I., Arvelo, F., Compagnone, R. S. New cytotoxic isoflavone from the root bark of *Brosimum utile*. *Nat. Prod. Res.*, **2005**, *19*, 331-335.

[66] Nakagawa-Goto, K., Bastow, K. F., Wu, J. H., Tokuda, H. and Lee, K. H. Total synthesis and bioactivity of unique flavone desmosdumotin B and its analogs. *Bioorg. Med. Chem. Lett.*, **2005**, *15*, 3016-3019.

[67] Nomura, M., Tsukada, H., Ichimatsu, D., Ito, H., Yoshida T., Miyamoto, K.I. Inhibition of epidermal growth factor-induced cell transformation by tannins. *Phytochmeistry*, **2005**, *66*, 2038-2046.

[68] Kumar, S., Singh, B.K., Pandey, A.K., Kumar, A., Sharma, S.K., Raj, H.G., Prasad, A.K., Van der Eycken, E., Parmarb V.S., Ghosh, B. A chromone analog inhibits TNF-a induced expression of cell adhesion molecules on human endothelial cells via blocking NF-jB activation. *Bioorg. Med. Chem.*, **2007**, *15*, 2952-2962.

[69] Semba, S., Itoh, N., Ito, M., harada M., Yamakawa, M. The *in vitro* and *in vivo* effects of 2-(4-morpholinyl)-8-phenylchromone (ly294002), a specific inhibitor of phosphatidylinositol 3_-kinase, in human colon cancer cells. *Clin. Cancer Res.*, **2002**, *8*, 1957-1963.

[70] Gamal-Eldeen, A.M., Abdel-Lateffand A., Okino, T. Modulation of carcinogen metabolizing enzymes by chromanone A; a new chromone derivative from algicolous marine fungus *Penicillium* sp. *Environ. Toxicol. Pharm.*, **2009**, *28*, 317-322.

[71] Brusselmans, K., Vrolix, R., Verhoeven G., Swinnen, J.V. Induction of cancer cell apoptosis by flavonoids is associated with their ability to inhibit fatty acid synthase activity. *J. Biol. Chem.*, **2005**, *280*, 5636-5645.

[72] Duraj, J., Zazrivcova, K., Bodo, J., Sulikova M., Sedlak, J. Flavonoid quercetin, but not apigenin or luteolin, induced apoptosis in human myeloid leukemia cells and their resistant variants. *Neoplasma*, **2005**, *52*, 273-279.

[73] Zhang, S.Z., Yang X.N., Morris, M.E. Combined effects of multiple flavonoids on breast cancer resistance protein (ABCG2)-mediated transport. *Pharmaceut. Res.*, **2004**, *21*, 1263-1273.

[74] Yoon, J.S., Lee, M.K., Sung S.H., Kim, Y.C. Neuroprotective 2-(2-Phenylethyl)chromones of *Imperata cylindrica*. *J. Nat. Prod.*, **2006**, *69*, 290-291.

[75] Baziard-Mouysset, G., Younes, S., Labssita, Y., Payard M., Caignard, D., Rettori, M., Renard, P., Pfeiffer, B., Guardiola-Lemaitre, B. Synthesis and structure-activity relationships of novel 2-amino alkyl chromones and related derivatives as CT site-selective ligands. *Eur. J. Med. Chem.*, **1998**, *33*, 339-347.

[76] Chen, I.S., Chang, C.T., Sheen, W.S., Teng, C.M., Tsa, I.L., Duh C.Y., Ko, F.N. Coumarins and antiplatelet aggregation constituents from formosan *Peucedanum japonicum*. *Phytochemistry*, **1996**, *41*, 525-530.

[77] Inaba, T., Tanaka, K., Takeno, R., Nagaki, H., Yoshida C., Takano, S. Synthesis and anti-inflammatory activity of 7-methanesulfonylamino-6-phenoxychromones. antiarthritic effect of the 3-formylamino compound (T-614) in chronic inflammatory cisease models. *Chem. Pharm. Bull.*, **2000**, *48*, 131-139.

[78] Koshy, A.S., Anila L., Vijayalakshmi, N.R. Flavonoids from Garcinia cambogia lower lipid levels in hypercholesterolemic rats. *Food Chem.*, **2001**, *72*, 289-294.

[79] Erickson, R.H., Natalie, K.J., Bock, W., Lu, Z., Farzin, F., Sherrill, R.G., Meloni, D.J., Patch R.J., Rzesotarski, W.J. (Aminoalkoxy) chromones. Selective sigma receptor ligands. *J. Med. Chem.*, **1992**, *35*, 1526-1535.

[80] Peixoto, F., Barros A.I.R.N.A., Silva, A.M.S. Interactions of a new 2-styrylchromone with mitochondrial oxidative phosphorylation. *J. Biochem. Mol. Toxicol.*, **2002**, *16*, 5220-226.

[81] Ueda, J., Imamura, L., Tezuka, Y., Tran, Q.L., Tsudab M., Kadot, S. New sesquiterpene from Vietnamese agarwood and its induction effect on brain-derived neurotrophic factor mRNA expression *in vitro*. *Bioorg. Med. Chem.*, **2006**, *14*, 3571-3574.

[82] Yagura, T., Ito, M., Kiuchi, F., Honda G., Shimada, Y. Four new 2-(2-Phenylethyl)chromone derivatives from withered wood of *Aquilaria sinensis*. *Chem. Pharm. Bull.*, **2003**, *51*, 560-564.

[83] Pontius, A., Krick, A., Kehraus, S., Foegen, S.E., Müller, M., Klimo, K., Gerhäuser, C., König, G.M. Noduliprevenone: a novel heterodimeric chromanone with cancer chemopreventive potential. *Chemistry*, **2008**, *14*, 9860-9863.

[84] Deschamps, J.D., Kenyon V.A., Holman, T.R. Baicalein is a potent *in vitro* inhibitor against both reticulocyte 15-human and platelet 12-human lipoxygenases. *Bioorg. Med. Chem.*, **2006**, *14*, 4295-4301.

[85] Chen, K.H., Wing, M.S., Lin, J.K. Tangeretin suppresses IL-1beta-induced cyclooxygenase (COX)-2 expression through inhibition of p38 MAPK, JNK, and AKT activation in human lung carcinoma cells. *Biochem. Pharmacol.*, **2007**, *73*(2), 215-727.

[86] Depypere H.T., Bracke, M.E., Boterberg, T., Mareel, M., Nuytunck, M., Vennekens K., Serreyn R. Inhibition of tamoxifen's therapeutic benefit by tangeretin in mammary cancer. *Eur J Cancer*, **2000**, *36*(4), S73.

[87] Manthey J.A., Guthrie, N. Antiproliferative activities of citrus flavonoids against six human cancer cell lines. *J. Agric. Food Chem.*, **2002**, *50*, 5837-5843.

[88] Morley, K.L., Ferguson P.J., Koropatnick, J. Tangeretin and nobiletin induce G1 cell cycle arrest but not apoptosis in human breast and colon cancer cells. *Cancer Lett.*, **2007**, *251*, 168-178.

[89] Ohnishi, H., Asamoto, M., Tujimura, K., Hokaiwado, N., Takahashi, S., Ogawa, K., Kuribayashi, M., Ogiso, T., Okuyama H., Shirai, T. Inhibition of cell proliferation by nobiletin, a dietary phytochemical associated with apoptosis and characteristic gene expression, but lack of effect on early rat hepatocarcinogenesis. *In Vivo Cancer Sci.*, **2004**, *95*, 936-942.

[90] Pan, M.H., Chen, W.J., Lin-Shiau, S.Y., Ho, C.T., Lin, J.K. Tangeretin induces cell-cycle G1 arrest through inhibiting cyclin-dependent kinases 2 and 4 activities as well as elevating Cdk inhibitors P21 and p27 in human colorectal carcinoma cells. *Carcinogenesis*, **2002**, *23*, 1677-1684.

[91] Yoshimizu, N., Otani, Y., Saikawa, Y., Kubota, T., Yoshida, M., Furukawa, T., Kumai, K., Kameyama, K., Fujii, M., Yano, M., Sato, T., Ito A., Kitajima, M. Anti-tumour effects of nobiletin, a citrus flavonoid, on gastric cancer include: antiproliferative effects, induction of apoptosis and cell cycle deregulation. *Aliment. Pharmacol. Ther.*, **2004**, *20*(1), 95-101.

[92] Vanhoecke, B.W., Delporte, F., Van Braeckel, E., Heyerick, A., Depyere, H.T., Nuytinck, M., De Keukeleire D., Bracke, M.E. A safety study of oral tangeretin and xanthohumol administration to laboratory mice. *In Vivo*, **2005**, *19*, 103-107.

[93] Conesa, C.M., Ortega, V.V., Gascon, M.J.Y., Banos, M.A., Jordana, M.C., Benavente-Garcia, O., Castillo, J. Treatment of metastatic melanoma B16F10 by the flavonoids tangeretin, rutin, and diosmin. *J. Agric. Food Chem.*, **2005**, *53*(17), 6791-6797.

[94] Datla, K.P., Christidou, M., Widmer, W.W., Rooprai, H.K., Dexter, D.T. Tissue distribution and neuroprotective effects of citrus flavonoid tangeretin in a rat model of Parkinson's disease. *Neuroreport*, **2001**, *12*(17), 3871-3875.

[95] Maiti, A., Cuendet, M., Kondratyuk, T., Croy, V.L., Pezzuto J.M., Cushman, M. Synthesis and cancer chemopreventive activity of zapotin, a natural product from *Casimiroa edulis*. *J. Med. Chem.*, **2007**, *50*, 350-355.

[96] Budzisz, E. Synthesis, reactions and biological activity of phosphorus-containing derivatives of chromone and coumarin. *Phosphorus Sulfur Silicon Relat. Elem.*, **2004**, *10*, 2131-2147.

[97] Gomes, A. Fernandes, E., Garcia, B.M., Silva, A.M.S., Pinto, D.C.G.A., Santos, C.M.M., Cavaleiro, J.A.S., Lima, J.L.F.C. Cyclic voltammetric analysis of 2-styrylchromones: relationship with the antioxidant activity. *Bioorg. Med. Chem.*, **2008**, *16*, 7939-7943.

[98] Shaw, A.Y., Chang, C.Y., Liau, H.H., Lu, P.J., Chen, H.L., Yang and C.N., Li, H.Y. Synthesis of 2-styrylchromones as a novel class of antiproliferative agents targeting carcinoma cells. *Eur. J. Med. Chem.*, **2009**, *44*, 2552-2562.

[99] Ueda, S. Nakamura, H. Masutani, H. Sasada, T. Takabayashi, A. Yamaoka Y., Yodoi, J. Baicalin induces apoptosis *via* mitochondrial pathway as prooxidant. *Mol. Immunol.*, **2002**, *38*, 781-791.

[100] Tian B., Hua, Y. Concentration-dependence of prooxidant and antioxidant effects of aloin and aloe-emodin on DNA. *Food Chem.*, **2005**, *91*, 413-418.

[101] An, R.B., Jeong, G.S., Beom, J.S., Sohn D.H., Kim, Y.C. Chromone Glycosides and Hepatoprotective Constituents of *Hypericum erectum*. *Arch. Pharm. Res.*, **2009**, *32*, 1393-1397.

[102] Yimam, M.A., Zhao, J., Tseng-Crank, J., Brownell, L., Devaraj, S., Jialal, R., Jialal, I., Rockwood, J., Ma, W., Padmapriya, A., Jia, Q. A novel standardized chromone extract (UP780) from Aloe regulated adiponectin production and improved insulin resistance. *Planta Med.*, **2008**, *74*(9), 926-926.

[103] Choi, S., Park, Y.I., Lee, S.K., Kim J.E., Chung, M.H. Aloesin inhibits hyperpigmentation induced by UV radiation. *Clin. Exp. Dermatol.*, **2002**, *27*, 513-515.

[104] Ma, L.Y. Ma, S.C., Wei, F., Lin, R.C., But, P.P.H., Lee S.H.S., Lee, S.F. Uncinoside A and B, Two new antiviral chromone glycosides from *Selaginella uncinata*. *Chem. Pharm. Bull.*, **2003**, *51*, 1264-1267.

[105] Hutter, J.A., Salman, M., Stavinoha, W.B., Satsangi, N., Williams, R.F., Streeper R.T., Weintraub, S.T. Anti-inflammatory C-glucosyl chromone from Aloe barbadensis. *J. Nat. Prod.*, **1996**, *59*, 541-543.

[106] Surjushe, A., Vasani R., Saple, D.G. Aloe vera: A short review. *Indian J. Dermatol.*, **2008**, *53*, 163-166.

[107] Radka, V., Ahcene, B., Marie, E., Jan K., Ivan, G. Modulation of paclitaxel transport by flavonoid derivatives in human breast cancer cells. Is there a correlation between binding affinity to NBD of P-gp and modulation of transport? *Bioorg. Med. Chem.*, **2006**, *14*, 4519-4525.

[108] Lamson D.W., Brignall, M.S. Antioxidants in cancer therapy; their actions and interactions with oncologic therapies. *Altern. Med. Rev.*, **1999**, *4*, 304-329.

[109] Linseisen J., Rohrmann, S. *Bioactive Components in Foods – Biomarkers of Dietary Polyphenol Intake for Studying Diet-Cancer Relationships. "Dietary Vitamins, Polyphenols, Selenium and probiotics: Biomarkers of Exposure and Mechanisms of Anticarcinogenic Action*, WP9 ECNIS Report – Mechanisms of Modulation of Cancer by Dietary Factors, Akesson, B., Mercke, P., Eds.; Nofer Institute of Occupational Medicine: Lodz, Poland, **2007**; pp. 64-70.

[110] Manson, M.M. In: *Bioactive Components in Foods – Anticarcinogenic Effects of Flavomoids. Dietary Vitamins, Polyphenols, Selenium and Probiotics: Biomarkers of Exposure and Mechanisms of Anticarcinogenic Action*, WP9 ECNIS Report – Mechanisms of Modulation of Cancer by Dietary Factors, Akesson, B., Mercke, P., Eds.; Nofer Institute of Occupational Medicine: Lodz, Poland, **2007**; pp. 115-122.

[111] Sancho, R., Marquez, N., Gomez-Gonzalo, M., Calzado, M.A., Bettoni, G., Coiras, M.T., Alcami, J., Lopez-Cabrera, M., Appendino, G., Munoz, E.J. Imperatorin inhibits HIV-1 replication through an Sp1-dependent pathway. *Biol. Chem.*, **2004**, *279*, 37349-37359.

[112] Kelland, L.R. Flavopiridol, the first cyclin-dependent kinase inhibitor to enter the clinic: current status. *Exp. Opin. Invest. Drugs*, **2000**, *9*, 2903-2911.

[113] Senderowicz, A.M. Flavopiridol: the first cyclin-dependent kinase inhibitor in human clinical trials. *Invest. New Drugs*, **1999**, *17*, 313-320.

[114] Senderowicz, A.M., Sausville, E.A. Preclinical and clinical development of cyclin-dependent kinase modulators. *J. Natl. Cancer Inst.*, **2000**, *92*, 376-387.

[115] Raju, U., Nakata, E., Mason, K.A., Ang, K.K., Milas, L. Flavopiridol, a cyclin-dependent kinase inhibitor, enhances radiosensitivity of ovarian carcinoma cells. *Cancer Res.*, **2003**, *63*, 3263-3267.

[116] Lopez-Lazaro, M. Flavonoids as anticancer agents: structure-activity relationship study. *Curr. Med. Chem.*, **2002**, *2*, 691-714.

[117] Heim, K.E., Tagliaferro A.R., Bobilya, D.J. Flavonoid antioxidants: chemistry, metabolism and structure-activity relationships. *J. Nutr. Biochem.*, **2002**, *13*, 572-584.

[118] Samee, W., Sae-Lee N., Ungwitayatorn, J. Structure-radical scavenging activity relationships of the synthesized chromone derivatives. *SWU J. Pharm. Sci.*, **2004**, *9*, 36-42.

[119] Boumendjel, A., Nicolle, E., Moraux, T., Gerby, B., Blanc, M., Ronot, X., Boutonnat, J., Piperazinobenzopyranones and phenalkylaminobenzopyranones: potent inhibitors of breast cancer resistance protein (ABCG2). *J. Med. Chem.*, **2005**, *48*, 7275-7281.

[120] Griffin, R.J., Fontana, G., Golding, B.T., Guiard, S., Hardcastle, I.R., Leahy, J.J.J., Martin, N., Richardson, C., Rigoreau, L., Stockley, M., Smith, G.C.M. Selective benzopyranone and pyrimido[2,1-*a*]isoquinolin-4-one inhibitors of dna-dependent protein kinase: synthesis, structure−activity studies, and radiosensitization of a human tumor cell line *in vitro*. *J. Med. Chem.*, **2005**, *48*, 569-585.

[121] Hadjeri, M., Barbier, M., Ronot, X., Mariotte, A. M., Boumendjel, A., Boutonnat, J. Modulation of P-glycoprotein-mediated multidrug resistance by flavonoid derivatives and analogues. *J. Med. Chem.*, **2003**, *46*, 2125-2131.

[122] Ishar, M.P.S., Singh, G., Singh, S., Sreenivasan, K.K., Singh, G. Design, synthesis, and evaluation of novel 6-chloro-/fluorochromone derivatives as potential topoisomerase inhibitor anticancer agents. *Bioorg. Med. Chem. Lett.*, **2006**, *16*, 1366-1370.

[123] Kim, Y.W., Hackett, J.C., Brueggemeier, R.W. Synthesis and aromatase inhibitory activity of novel pyridine-containing isoflavones. *J. Med. Chem.*, **2004**, *47*, 4032-4040.

[124] Kim, K.S., Sack, J.S., Tokarski, J.S., Qian, L., Chao, S.T., Leith, L., Kelly, Y.F., Misra, R.N., Hunt, J.T., Kimball, S.D., Humphreys, W.G., Wautlet, B.S., Mulheron, J.G., Webster, K.R. Thio- and oxoflavopiridols, cyclin-dependent kinase 1-selective inhibitors: synthesis and biological effects. *J. Med. Chem.*, **2000**, *43*, 4126-4134.

[125] Lindell, S.D., Ort, O., Lummen, P., Klein, R. The design and synthesis of novel inhibitors of NADH:ubiquinone oxidoreductase. *Bioorg. Med. Chem. Lett.*, **2004**, *14*, 511-514.

[126] Schoepfer, J., Fretz, H., Chaudhuri, B., Muller, L., Seeber, E., Meijer, L., Lozach, O., Vangrevelinghe, E., Furet, P. Structure-based design and synthesis of 2-benzylidene-benzofuran-3-ones as flavopiridol mimics. *J. Med. Chem.*, **2002**, *45*, 1741-1747.

[127] Chen, D., Dou, Q.P. New uses for old copper-binding drugs: converting the pro-angiogenic copper to a specific cancer cell death inducer. *Expert Opin. Ther. Targets*, **2008**, *12*(6), 739-748.

[128] Cvek B., Dvorak Z.T. Targeting of nuclear factor-κB and proteasome by dithiocarbamate complexes with metals. *Curr. Pharm. Des.*, **2007**, *13*(30), 3155-3167.

[129] Milacic, V., Chen, D., Ronconi, L., Landis-Piwowar, K.R., Fregona D., Dou, Q.P. A novel anticancer gold(III) dithiocarbamate compound inhibits the activity of a purified 20S proteasome and 26s proteasome in human breast cancer cell cultures and xenografts. *Cancer Res.*, **2006**, *66*(21), 10478-10486.

[130] Zhang, H., Jiu-Sheng W., Peng, F. Potent anticancer activity of pyrrolidine dithiocarbamate-copper complex against cisplatin-resistant neuroblastoma cells. *Anticancer Drugs*, **2008**, *19*(2), 125-132.

[131] Roy, K., Mitra, I. Advances in quantitative structure-activity relationship models of antioxidants. *Exp. Opin. Drug Discov.*, **2009**, *4*(11), 1157-1175.

[132] Cheng, Z., Ren, J., Li, Y., Chang, W., Chen, Z. Study on the multiple mechanisms underlying the reaction between hydroxyl

radical and phenolic compounds by quantitative structure and activity relationship. *Bioorg. Med. Chem.*, **2002**, *10*, 4067-4073.

[133] Fang, H., Tong, W., Shi, L.M., Blair, R., Perkins, R., Branham, W., Hass, B.S., Xie, Q., Dial, S.L., Moland C.L., Sheehan, D.M. Structure-activity relationships for a large diverse set of natural, synthetic, and environmental estrogens. *Chem. Res. Toxicol.*, **2001**, *142*, 280-294.

[134] Fiorucci, S., Golebiowski, J., Cabrol-Bass D., Antonczak, S. Oxygenolysis of flavonoid compounds: dft description of the mechanism for quercetin. *Chem. Phys. Chem.*, **2004**, *5*(11), 1726-1733.

[135] Gupta, S., Matthew, S., Abreu, P.M., Aires-de-Sousa, J. QSAR analysis of phenolic antioxidants using MOLMAP descriptors of local properties. *Bioor. Med. Chem.*, **2006**, *14*, 1199-1206.

[136] Reis, M., Lobato, B., Lameira, J., Santos, A.S., Alves, C.N. A theoretical study of phenolic compounds with antioxidant properties. *Eur. J. Med. Chem.*, **2007**, *42*, 440-446.

[137] Selassie, C.D., Kapur, S., Verma R.P., Rosario, M. Cellular apoptosis and cytotoxicity of phenolic compounds: a quantitative structure-activity relationship study. *J. Med. Chem.*, **2005**, *48*, 7234-7242.

[138] Amić, D., Davidović-Amić, D., Bešlo, D., Rastija, V., Lučić B., Trinajstić N. SAR and QSAR of the antioxidant activity of flavonoids. *Curr. Med. Chem.*, **2007**, *14*, 827-845.

[139] Amić, D., Davidović-Amić, D., Bešlo, D., Trinajstić, N. Structure-radical scavenging activity relationships of flavonoids. *Croat. Chem. Acta*, **2003**, *76*, 55-61.

[140] Farkas, O., Jakus, J., Héberger, K. Quantitative structure-activity relationship analysis of flavonoid compounds. *Molecules*, **2004**, *9*, 1079-1088.

[141] Lemańska, K., Szymusiak, H., Tyrakowska, B., Zieliński, R., Soffers, A.E.M.F., Rietjens, I.M.C.M. The influence of pH on antioxidant properties and the mechanism of antioxidant action of hydroxyflavones. *Free. Radic. Biol. Med.*, **2001**, *31*, 869-881.

[142] Ungwitayatorn, J., Samee, W., Pimthon, J. 3D-QSAR studies on chromone derivatives as HIV-1 protease inhibitors. *J .Mol. Struct.*, **2004**, *689*, 99-106.

[143] Nunthanavanit, P., Nahoum, G.A., Johnston, B.F., Mackay, S.P., Ungwitayatorn, J. 3D-QSAR studies on chromone derivatives as HIV-1 protease inhibitors: application of molecular field analysis. *Arch. Pharm. Chem. Life Sci.*, **2008**, *341*, 357-364.

[144] Sadeghipour, M., Terreux R., Phipps, J. Flavonoids and tyrosine nitration: structure–activity relationship correlation with enthalpy of formation. *Toxicol. In Vitro*, **2005**, *19*, 155-165.

[145] Samee, W., Nunthanavanit P., Ungwitayatorn, J. 3D-QSAR investigation of synthetic antioxidant chromone derivatives by molecular field analysis. *Int. J. Mol. Sci.*, **2008**, *9*, 235-246.

[146] Khlebnikov, A.I., Schepetkin, I.A., Domina, N.G., Kirpotina, L.N., Quinn, M.T. Improved quantitative structure-activity relationship modles to predict antioxidant activity of flavonoids in chemical, enzymatic, and cellular systems. *Bioorg. Med. Chem.*, **2007**, *15*, 1749-1770.

[147] Rice-Evans, C.A., Miller, N.J., Paganga, G. Structure-antioxidant activity relationships of flavonoids and phenolic acids. *Free Radic. Biol. Med.*, **1996**, *20*, 933-956.

[148] Lai H.H., Yen, G.C. Inhibitory effect of isoflavones on peroxynitrite-mediated low-density lipoprotein oxidation. *Biosci. Biotechnol. Biochem.*, **2002**, *66*, 22-28.

[149] Dueñas, M., González-Manzano, S., González-Paramás, A., Santos-Buelga C. Antioxidant evaluation of O-methylated metabolites of catechin, epicatechin and quercetin. *J. Pharm. Biomed. Anal.*, **2010**, *51*, 443–449.

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