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REVIEW

Human health-related properties of chromones: an overview

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ABSTRACT

Natural compounds occurring throughout the world are scientifically and practically valuable because of their unique and beneficial properties to control a wide range of disorders in the human body. Chromones are attracting increasing attention as novel therapeutic agents due to their effective bioactivities for human health. Accordingly, the present overview article was designed to scan the biological and pharmacological performance of chromones, including their anti-inflammatory, anticancer, anti-oxidant, and anti-microbial activities.

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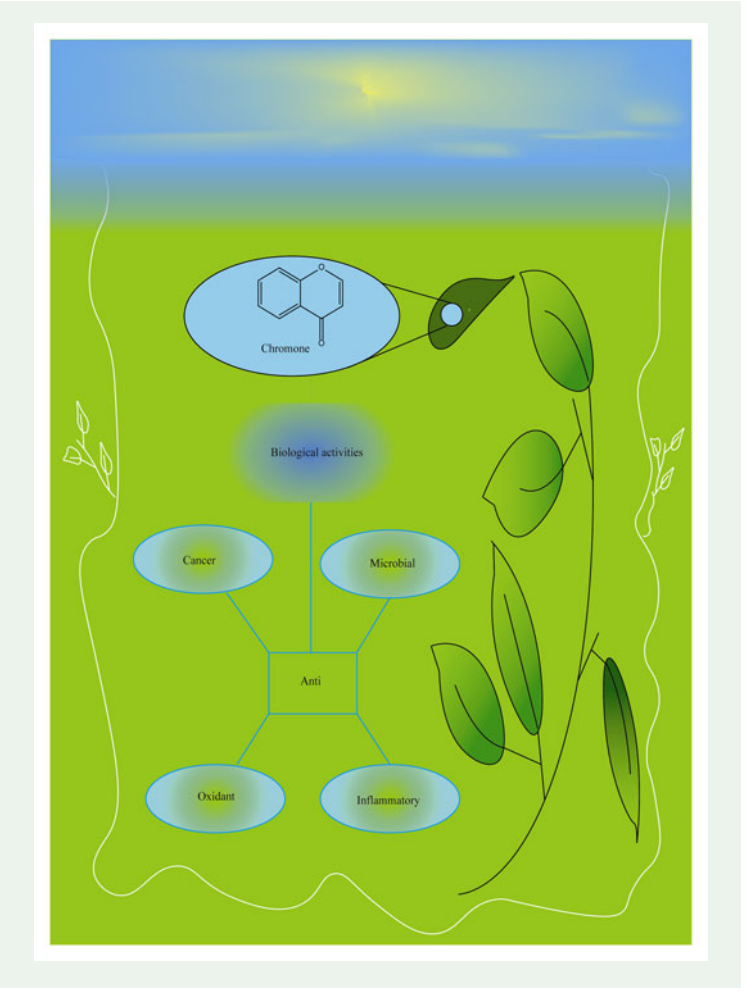

1. Introduction

Natural products with a diverse structure and function occurring throughout the world today are considered as suitable candidates for the substitution of synthetic drugs used for a wide range of diseases that may come with serious and different side effects as well as heavily influencing the therapeutic costs for the national health system. Nonetheless they also impact on society and patients, being necessary to assess proper and scientifically substantiated information and also taking into proper account both adherence and compliance to suggested pharmacological therapies (Abenavoli et al. 2018; Andrew and Izzo 2017; Coretti et al. 2015; Daliu et al. 2018; 2019; Durazzo et al. 2018; Durazzo et al. 2018; Durazzo et al. 2019; Kumari and Singh 2019; Menditto et al. 2018; Salehi et al. 2019a; Salehi et al. 2019b; Santini and Novellino 2014; Santini and Novellino 2017; Santini and Novellino 2018; Santini et al. 2017; Santini et al. 2018; Scala et al. 2016). Among these, chromones and corresponding derivatives as heterocyclic compounds and secondary metabolites in plants have attracted further attention

due to the broad spectrum of therapeutic and pharmacological properties and high potency of bioactivity (Boniface and Igne-Ferreira 2019; Edwards 2000; Gaspar et al. 2014; Huang et al. 2019; Hiruy et al., 2019; Keri et al. 2014; Matos et al. 2015; Sharma et al. 2011). Accordingly, this overview article was designed to explore some of the main biological and pharmacological performance of chromones, including anti-inflammatory, anti-oxidant, anticancer, and anti-microbial activities as well as the techniques examined to promote these functions.

2. Chromone class: a snapshot of chemical features

Chromone (1,4-benzopyrone) is a derivative of benzopyran with a substituted keto group on the pyran ring. The chromone moiety is the essential component of pharmacophores of a large number of bioactive molecules. Reis et al. 2017 underlined how chromone has a privileged structure for the design of novel compounds with potential pharmacological interest (Reis et al. 2017). Several current researches have focused on fictionalization of chromone mojety (DeRatt et al. 2019) and the synthesis of scaffolds (Kumar et al. 2019). On the other hand, it is worth mentioning the recent review of Vanguru et al. 2018 on the synthetic methodologies of chromones (Vanguru et al. 2018).

3. The anti-cancer properties

Cancer, despite being one of the major global health concerns associated with mortality and morbidity, has limited therapies, highlighting the need to develop effective anticancer drugs. The chromone and related derivatives have been recently recognized to be effective natural compounds against a wide range of cancers with a variety of functions (Duan et al. 2019; Vanguru et al. 2018), for example, drug carriers (Baráth et al. 2006; Krapf et al. 2017; Obreque-Balboa et al. 2016, Figure 1, (7); Valdameri et al. 2012, Figure 1, (6)), thymidine phosphorylase (Khan et al., 2009, Figure 1, (1)), protein tyrosine phosphatases (Forghieri et al. 2009), topoisomerases (Ishar et al. 2006; Maicheen et al. 2013) and protein kinases (Kumar et al. 2007). See Figure 1 for more information.

Demir et al. (2019) evaluated the anticancer activity of furochromone derivatives in various body tissues. They reported that ethyl 2-(5-((4, 9-dimethoxy-5-oxo-5*H*-furo[3,2-*g*]chromen-7-yl)methylene)-4-oxo-2-thioxothiazolidin-3-yl)acetate at a concentration $\leq$10μM was comparatively able to control the breast cancer cells (Figure 1 (2)). As shown in Figure 1, (9), others after preparing novel furopyranone-chromone conjugate and furocoumarin-chromone conjugate exhibited capability of preventing the cancer cells for the 4I and 4 K compounds with the IC_{50} values of 2.72 μg/ml and 2.56 μg/ml, respectively (Meydani et al. 2019). Elsayed et al. (2015) found the IC_{50} values of 1 and 0.87 μM for the [Ag(*fcbh*) (*PPh3*)] complex to control the cell lines of human breast cancer (MDA- MB231) and human ovarian cancer (OVCAR-8), respectively. Yousuf et al. (2015) studied the chromone-appended Cu (II) (3) drug cytotoxicity on breast carcinoma (MCF-7) and hepatocarcinoma (HepG2) cell lines (Figure 1). According to their results, the IC_{50} values were different between 5.0 and 10 μg/ml. In a study by

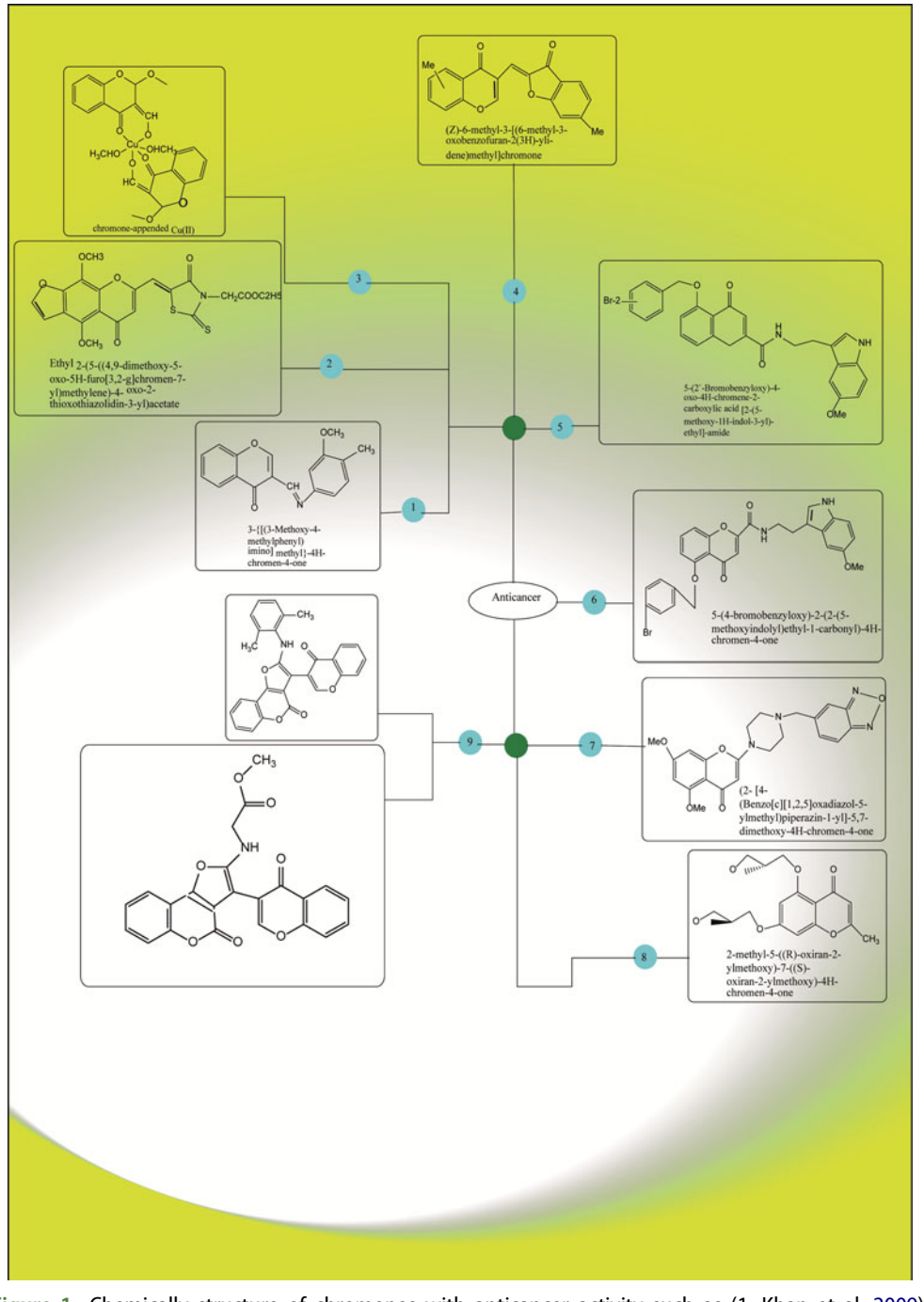

Figure 1. Chemically structure of chromones with anticancer activity such as (1, Khan et al. 2009), (2, Demir et al. 2019), (3, Yousuf et al. 2015), (4, Zwergel et al. 2013), (5, Pires et al. 2016), (6, Valdameri et al. 2012), (7, Obreque-Balboa et al. 2016), (8, Jo et al. in 2019), (9, Meydani et al. 2019).

Kowalski et al. (2013), the (*E*)-6-ferrocenylvinyl-chromen-4-one exerted cytotoxicity on T lymphoblast-like polymorph cells (CCRF-CEM). Zwergel et al. (2013) employed the coumarin-based benzofuran and chromone-based benzofuran derivatives ((*Z*)-6-methyl-3-[(6-methyl-3-oxobenzofuran-2(3*H*)-yli- dene)methyl]chromone, (*Z*)-7-methoxy-4-[(6-methyl-3-oxobenzofuran-2(3*H*)-yli-dene)methyl]-2*H*-coumarin and (*Z*)-2-[(7-methoxycoumarin-yl)methylene]naphtho[2,3 *b*]-furan-3(2*H*)-one) and reported about 24% apoptosis for k562 leukemia cells (Figure 1, (4)). In screening potential compounds to inhibit the human breast cancer, 5-aminochromones and 1-amino- xanthones showed anticancer activity (Shin et al. 2014). The chromones bearing various dithiocarbamate moieties have opened promisingly new windows to control some cancers (Huang et al. 2009), including MDA-MB-435S (mammary adenocarcinoma), and SW-480 (colon carcinoma) arrested in G2/M phase by(6-chloro-4-oxo-4*H*-chromen-3-yl)-methyl piperidine-1-carbodithioate (IIu) and (3-chloro-4-oxo-4*H*-chromen-2-yl)methyl piper- idine-1-carbodithioate (Iq) compounds.

Protein kinases possess regulatory action on many signaling pathways, suggesting their function as anticancer properties (Zhao et al. 2019). Amin et al. (2018) studied the capability of 4-fluorophenyl-2-iminopyridine-benzofuran-4-compound in controlling the MAP kinase p38α. They applied MTT technique and found this compound with ability to suppress the MCF-7 cell line in the G2/M phase. The benzofuran derivatives impeded endothelial growth factor receptor, VEGFR-2 (Abdelhafez et al. 2015), so that bromo-4-methoxy-7- methyl-5*H*-furo[3,2-g]chromen-5-one compound, exhibited antiprostate cancer activity and high anti-VEGFR-2 activity with best IC_{50} values.

Mao and Unadkat (2015) reported that the ATP-Binding Cassette (ABC) carriers are membrane protein capable of cell supporting through directing the toxic agents out of the cell, most important of which are breast cancer resistant protein (BCRP/ABCG2/MXR), multidrug resistance protein 1 (MRP1/ABCC1) and P-glycoprotein (P-gp/ABCB1/MDR1) (Mao and Unadkat 2015). The irinotecan (CPT-11) combined with 5-(4-bromobenzyloxy)-2-(2-(5-methoxyindolyl) ethyl-1-carbonyl)-4*H*-chromen-4-one reported blocked the ABCG2-positive xenografts (Payen et al. 2015). The 5-(4-bromobenzyloxy)-2-(2-(5-methoxyindolyl)ethyl-1-carbonyl)-4*H*-chromen-4-one as a novel chromone derivative was introduced by Winter et al. (2013), which could block breast Cancer Resistance Protein ABCG2 generated by central amide nitrogen methylation, position five substitution of 4-bromobenzyloxy, and the methoxyindole. The compound 5-(2-Bromobenzyloxy)-4-oxo-4*H*-chromene-2-carboxylic acid [2-(5-methoxy-1*H*-indol-3-yl)-ethyl]-amide was synthesized by mounting a 2-bromine atom on benzyloxy group of chromone-derived compound (MBL-II-141), which showed higher activity in preventing ABCG2 in comparison with others (Pires et al., 2016) (Figure 1, (5)).

The topological problems during the separation of DNA strands within transcription and replication can be resolved by topoisomerases (topo). Jo et al. (2019) introduced a new compound containing epoxy and halohydrin substituents with chirality, among which 2-methyl-5-((*R*)-oxiran-2-ylmethoxy)-7-((*S*)-oxiran-2-ylmethoxy)-4*H*-chromen-4-one compound strongly inhibited the topo I and topo IIα and, K562 myelogenous leukemia cancer cell proliferation with IC_{50} value of 0.04 μM (Figure 1, (8)). RuII (Ⅱ]6-p-cymene)-

chromone as new compound was able to block the topoisomers I and to exhibit the anticancer activity (Yousuf et al. 2019).

4. The anti-inflammatory properties

The chromones showed reportedly anti-inflammatory function *via* the inhibition of various mechanisms, including intercellular adhesion molecule inhibitors, mast cell stabilizers, cyclooxygenase inhibitors (Gautam et al. 2011; Jachak et al. 2011; Shaveta et al. 2014) (Figure 2, 1), leukotriene receptor antagonists, interleukin-5 inhibitors (Joo et al. 2012; Thanigaimalai et al. 2010; Venkateswararao et al. 2013; Venkateswararao et al. 2015, Figure 2, (2)) (Figure 2), lipoxygenase inhibitors (Altavilla et al. 2009; Ribeiro et al., 2014), and Nitric oxide (NO) production inhibitors (An et al. 2015 Figure 2, (5); Chen et al. 2012; Forstermann and Sessa 2012; Gao et al. 2014; Jia et al. 2014; Kim et al. 2015 Figure 2, (4); Liu et al. 2010, Figure 2, (3); Pham et al. 2012;) (Figure 2). It should be noted that these anti-inflammatory properties of the chromones have been utilized with clinical purposes, including cancer, rheumatoid arthritis, neurodegenerative diseases, neuropathies, and asthma (Mantovani et al. 2011; Silva et al. 2016). Huo et al. (2019) reported the inhibition of NO formation by 2-(2-phenylethyl)chromone dimers with IC_{50} values ranging from 0.6 to 37.1 μM, derived from Chinese agarwood, Aquilaria sinensis. Moreover, 5-*O*-methylcneorumchromone K was derived from Dictyoloma vandellianum root bark, which displayed anti-inflammatory function *via* the activation of a glucocorticoid receptor RU486 (Opretzka et al. 2019). The activity of COX inhibitor was reported for compounds formed from combining pyrazole, indole and chrysin (Singh et al. 2014).

5. The anti-microbial properties

The infectious diseases have been recently increasing due to elevated resistance to human pathogens, thereby imposing huge medical concerns. Therefore, strong strategies are needed to deal with this serious risk, which can be achieved by new antimicrobial agents. There are some drugs against resistant infections, for example, those based on the chromone structure (Cano et al. 2015, Figure 3, (4); He et al. 2018, Figure 3, (1)). Hiruy et al. (2019) reported the extraction of compounds derived from the leaf latex of Aloe monticola Reynolds, including Aloesin and 7-O-methyl-60-O-coumaroylaloesin, with antimicrobial properties (Figure 3, (2)). Li et al. (2008) found inhibitory effect of chromone derivative from the Fungus *Chaetomium brasiliense* against human lung (Lu04), human neuroma (N04) and human breast cancer (Bre04). In a study by Huang et al. (2017), (2′*S**)-2-(2′-hydroxypropyl)-5-methyl-7, 8-dihydroxy-chromone from the mangrove-derived fungus *Penicillium aculeatum* exhibited anti-bacterial function with a MIC value of 2.00 ± 0.02 μM (Figure 3, (3)).

6. The anti-oxidant properties

DNA, lipoproteins, lipids and proteins are affected by the oxidative damage resulting from potentially toxic and reactive oxygen moieties of reactive oxygen species (ROS).

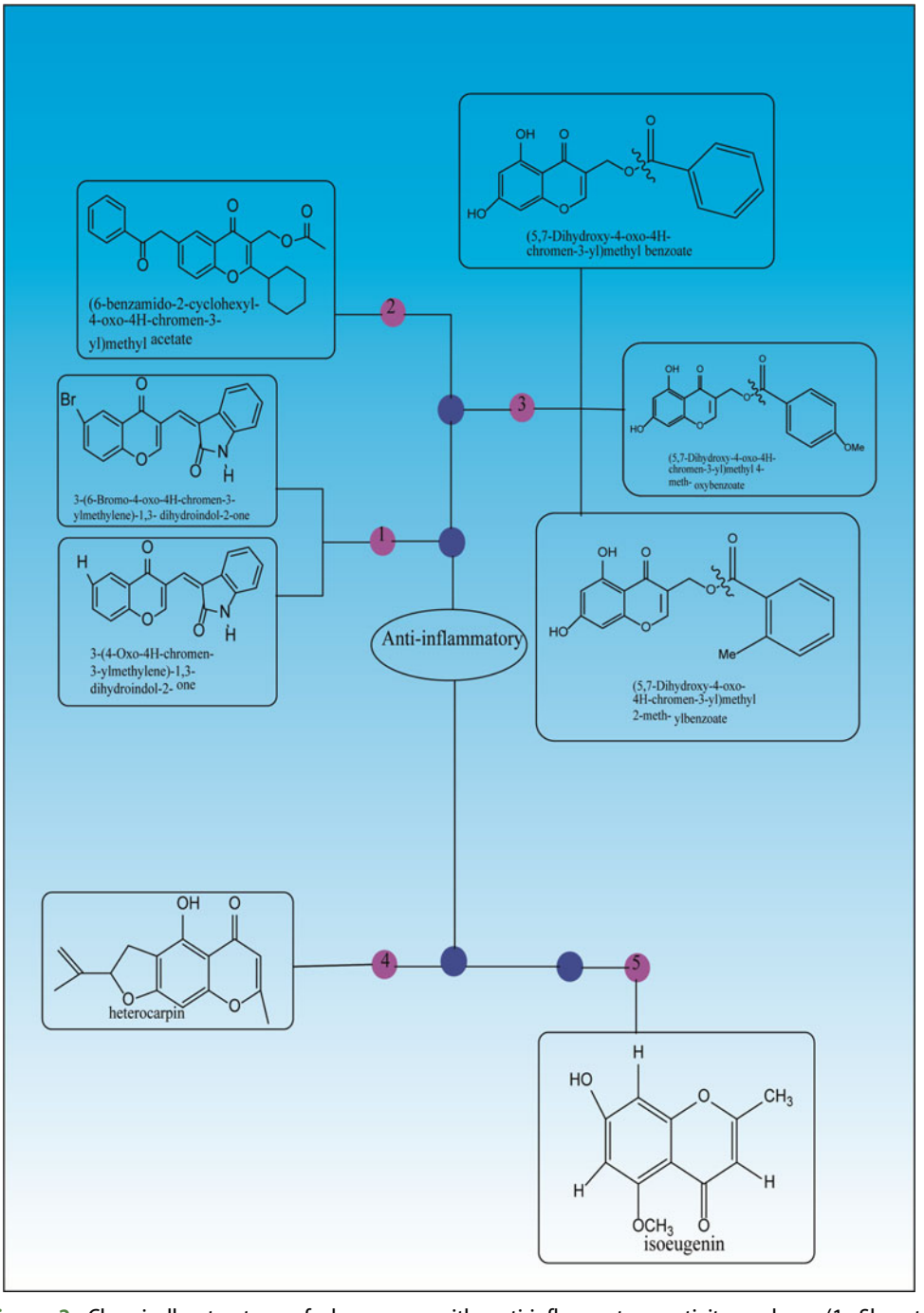

Figure 2. Chemically structure of chromones with anti-inflammatory activity such as (1, Shaveta et al. 2014), (2, Venkateswararao et al. 2015) (3, Liu et al. 2010), (4, Ma et al. 2015), (4, Kim et al. 2015), and (5, An et al. 2015).

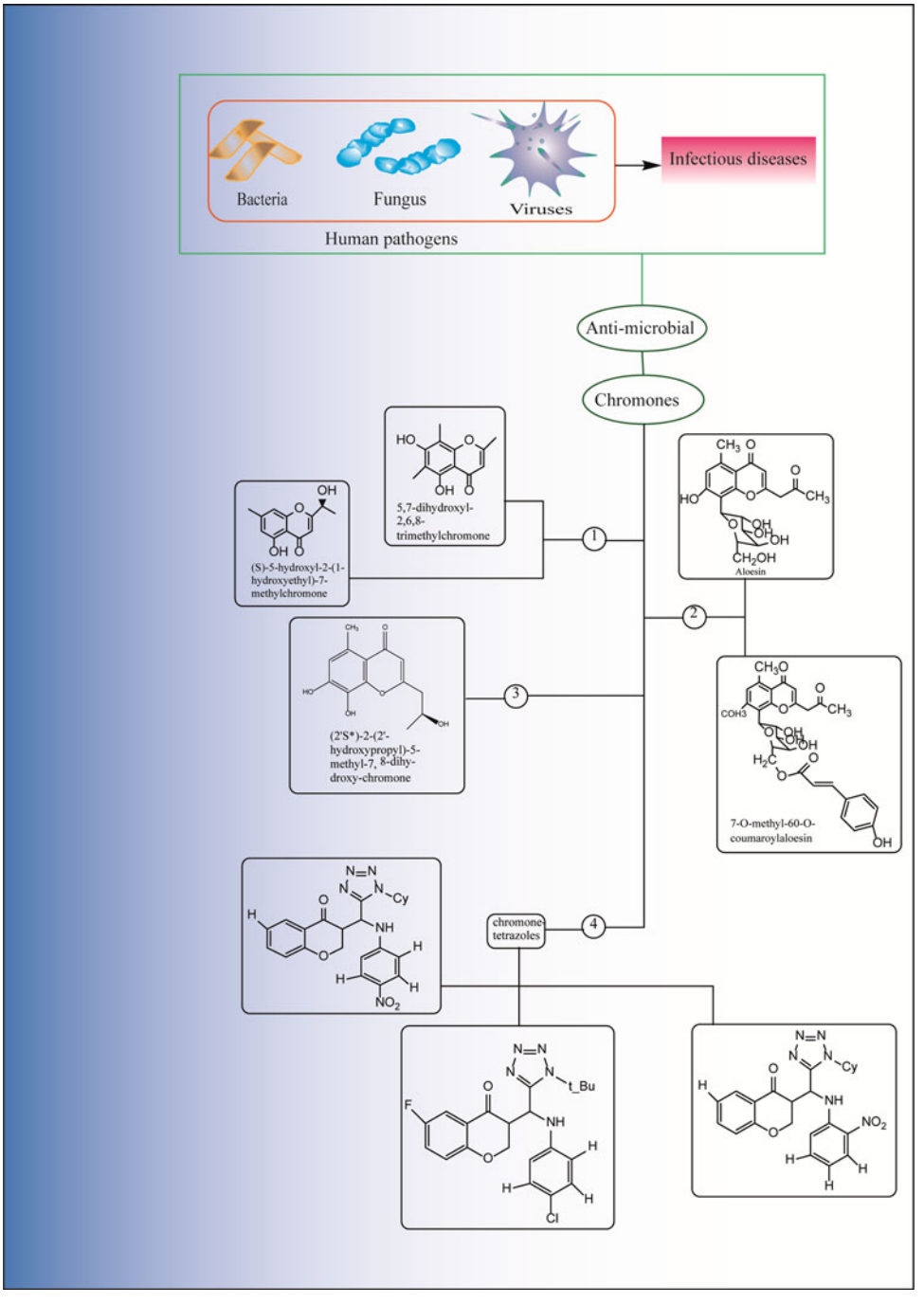

Figure 3. Chemically structure of chromones with anti-microbial activity such as (1, He et al. 2018), (2, Hiruy et al. in 2019), (3, Huang et al. 2017), and (4, Cano et al. 2015).

The anti-oxidant compounds in food groups have attracted further attention in human health (Durazzo 2017; Durazzo 2018; Durazzo and Lucarini 2019; 2019). The antioxidants not only can decrease lipid peroxidation activity and chronic disease progression

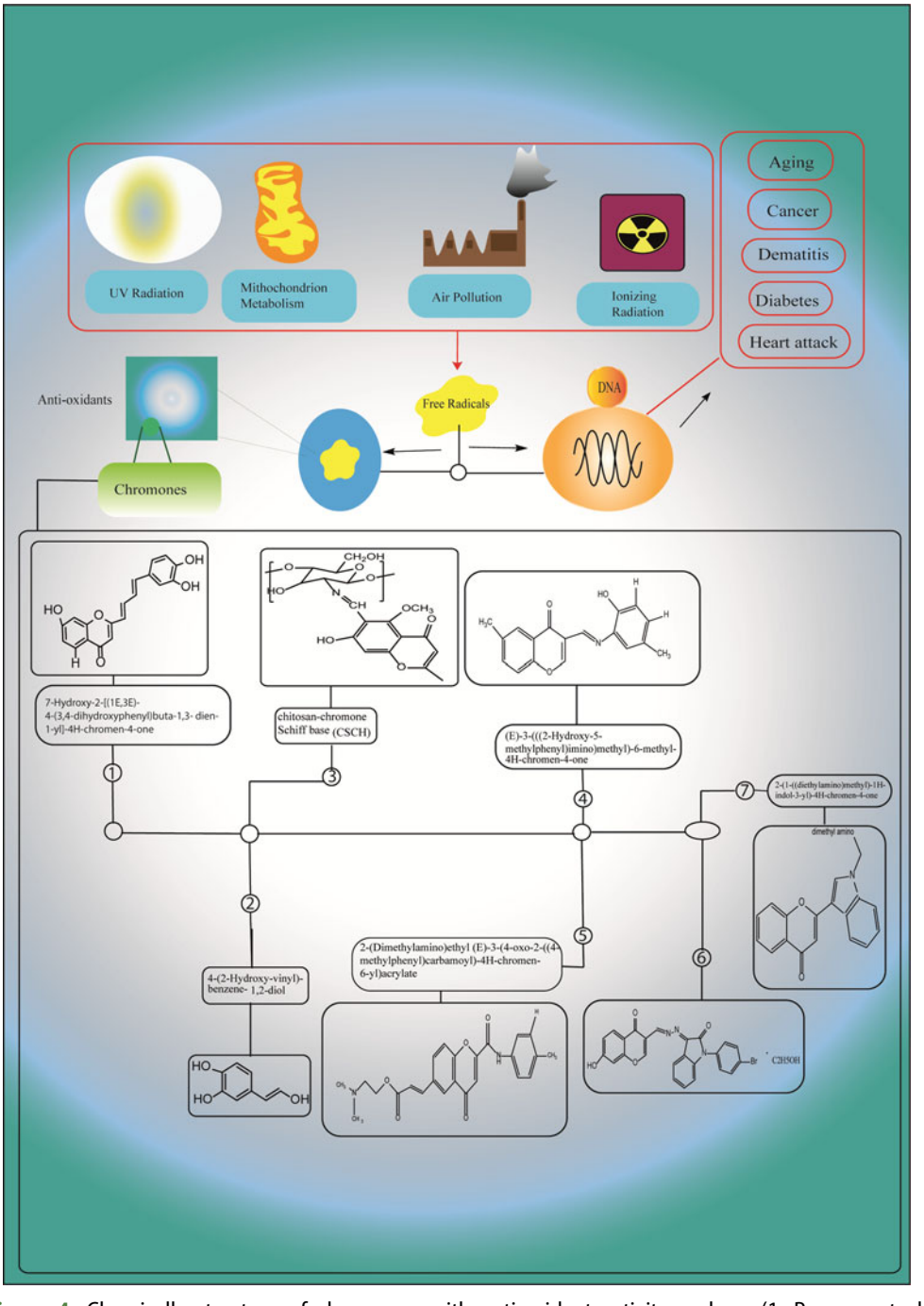

Figure 4. Chemically structure of chromones with anti-oxidant activity such as (1, Proença et al. 2016), (2, Grażul et al. 2012), (2, Park et al. 2007), (4, Gamal-Eldeen et al. 2009), (3, Demetgül and Beyazit 2018), (4, Li et al. 2017), (5, Reis et al. 2018), (6, Wang et al. 2018), (7, Valentina et al. 2017).

(like heart disease, cancer, and diabetes), but also can protect the human body against the ROS and free radicals. There are many studies reporting effective antioxidant activity of the chromones (Grażul et al., 2012; Kang et al. 2008; Kuroda et al. 2009; Park et al. 2007, Figure 4, (2); Phosrithong et al. 2012; Proença et al., 2016, Figure 4, (1); Yimam et al. 2015) (Figure 4); for examples, Csepanyi et al. (2017) found the anti-oxidant activity of 4-*N*,*N*-dimethyl amino -flavon, and Demetgül and Beyazit (2018) reported the anti-oxidant activity of chromone-chitosan Schiff base (CSCH) compound (Figure 4, (3)). Alzheimer's disease (AD) as one of the neurodegenerative conditions is induced by a redox imbalance. Reis et al. (2018) introduced a new chromone-based library to impede the monoamine oxidases and cholinesterases in human samples. Thus, they considered a phenylcarboxamide moiety at position C2- or C3 and a tertiary amine of an acrylate moiety at position C6 to functionalize the chromone scaffold, followed by developing putative metabolites through the hydrolysis of acrylate side chain. Their findings demonstrated AChE (IC_{50}:0.21), MAO-B (IC_{50}:3.81 ± 0.01 μM) and MAO-A (IC_{50}:0.94 ± 0.03 μM) inhibitory function for 2-(dimethylamino) ethyl (*E*)-3-(4-oxo-2-(pmethylphenlcarbamoyl)-4*H*-chromen-6-yl) acrylate compound (Figure 4, (5)). Li et al. (2017) computed the IC_{50} value of 5.12 lM for hMAO-A and the IC_{50} value of 0.816 lM for hMAO-B regarding a novel compound ((*E*)-3-(((2-Hydroxy-5-methylphenyl)imino)methyl)-6-methyl-4*H*-chromen-4-one) derived from chromone (Figure 4, (4)). The postprandial hyperglycemia in the diabetic patients can be conventionally managed by the delayed glucose uptake through the inhibition of α-amylase enzyme. In this regard, Valentina et al. (2017) evaluated the inhibitory function of (1-((diethylamino) methyl)-1*H*-indol-3-yl)-4*H*-chromen-4-one (Figure 4, (7)). Wang et al. (2018) found the capability of impeding α-glucosidase enzyme by chromone-isatin derivatives. Among which, the compound (6j) containing a hydroxyl group at the 7-position of chromone and 4-bromobenzyl group at the N1-positions of isatin exhibited the IC_{50} value of 3.18 ± 0.12 lM (Figure 4, (6)).

7. Conclusion

The data reported in the present overview outline the fact that there are numerous documents regarding the possible health impact of chromone and its derivatives. In fact some of them are currently widely used both for the development of novel pharmaceuticals and as model to discover novel synthetic drugs. Despite the existing reports of a limited therapeutic value for chromones, they are potentially suitable candidates for producing effective drugs. Therefore, targeted changes in the structure of these compounds can result in the development of parental molecules and drugs (Silva et al., 2018). The present article presents reports on the capability of different structures of chromones and their beneficial effects to treat broad spectrum of diseases, as well as on the techniques used to promote the performance of these compounds. The reported data could trigger further interest in research on developing molecules with improved bioactivities and pharmacological potential.

Disclosure statement

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