Antioxidant Drug Design: Historical and Recent Developments

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Review Article

ABSTRACT

The sustained interest in the design of potent antioxidants drugs over the years can be attributed to the indispensable roles antioxidants play in the mitigation of oxidative stress and its concomitant diseases. The high demand for exogenous antioxidants has been ascribed to the prevalence of oxidative stress-mediated diseases such as cancer, diabetes, stroke, cell aging, arteriosclerosis and central nervous system disorders occasioned by a biochemical disequilibrium between the production of free radicals and the body's ability to eliminate these reactive species from the biological system. COVID-19 severity and death have been linked to a free radical generating process known as the cytokine storm. In an attempt to maintain optimal body function, antioxidant supplementation has increasingly become a wide spread practice because of antioxidants' ability to

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directly scavenge free radicals, inhibit oxidative chain reactions thereby increasing the antioxidant defenses of the body. Recent data showed that researchers had made significant efforts to demonstrate the importance and timeliness of antioxidant therapy based on drug design from natural and synthetic sources. Therefore this review presents antioxidant drug design methodologies, identifying the lead and hits to provide a historical and up-to-date collection of research briefs on antioxidant drug design into a single piece in order to ensure easy accessibility, motivate readership and inspire future researches.

1. INTRODUCTION

Historically, the word "antioxidant" was first used in the 19th century to describe any substance with the ability to hinder oxygen consumption. Antioxidants' applications were industrial, for vulcanization of rubber, corrosion inhibition, and polymerization [1]. Biologically, antioxidants were employed in the inhibition of rancidity of unsaturated fats [2]. In the early 20th century, Moses Gombery, a chemistry professor discovered the first organic free radicals, triphenylmethyl and vitamin E and C were consequently identified as antioxidants. This discovery portrays antioxidants in good light and brought revolution to the field of biochemistry of living organisms [3,1] The mechanism of action of antioxidants was explored and they were identified as reducing agents [4-5]. Antioxidants are defined as compounds that inhibit free-radical generating chemical reactions. They bind to free radicals so as to prevent them from damaging biological molecules [6]

Research on the discovery of natural and synthetic antioxidants drugs design extensively carried out, but there is a lack of single papers with a collection of antioxidant drug design methodologies, design leads, and antioxidants' role in disease therapy. This review presents a collection of research briefs on the design of antioxidant drugs and transformational approaches that enable the modification of antioxidant leads to improved potency and therapeutic applications.

2. ANTIOXIDANT FUNCTIONS

Biochemically and physiologically, biological systems develop a balanced redox state as a defense mechanism in an aerobic environment [7]. This typically involve the micro-vascular, enzymatic or nonenzymatic systems of the organism. These systems work in synergy to protect the cells, tissue and organs from free radicals' destructive effects. Ideally, antioxidants eliminate reactive oxygen species (ROS), chelate redox metals, work effectively in the aqueous and membrane domain and positively affect organism's gene expression. Antioxidants neutralize and eliminate ROS by decreasing the oxygen level, transforming radicals to nonradicals or inhibit the initiation stage of hydroxyl radical ($^{.}OH$) formation. Antioxidants exhibit three major defence systems. The first involves antioxidant enzymes. The second involves elemental ions binding proteins such as transferrin and albumin. These binding proteins suppress the formation of free radicals and hinder their adverse reaction with biochemical molecules. The third defense system involves the scavenging of free radicals even in low quantities. The endogenous enzymatic antioxidants such as catalase (CAT), glutathione peroxidase (GSH-Px) and superoxide dismutase (SOD) suppress adverse reactions of free radicals by metabolizing the free radicals into harmless substances [8]. Conversely, exogenous antioxidants such as polyphenols, carotenoids, vitamin A, C, E and xanthophylls function by directly participating in a redox reaction with the free radicals to prevent cell death and enhance DNA repair processes [9-10].

3. ANTIOXIDANT SUPPLEMENTATION

The prevalence of oxidative stress-mediated diseases due to over-population, pollution, climatic change, changes in eating habits and other factors that over burden the biological system with free radicals have necessitated extensive research on the impact of antioxidant supplementation on health [11]. Though organisms are well equipped with some effective enzymatic and nonenzymatic endogenous antioxidants become inadequate for the maintenance of normal redox status in the case of increased free radicals, and this results in oxidative stress. In such cases, supplementation with exogenous antioxidants becomes inevitable for stable redox homeostasis in cells [12].

Although the efficacy of antioxidant supplementation against oxidative stress and related diseases has been controversial, it has become a wide spread practice for the maintenance of optimal body function [13-15]. Several studies indicated that prolonged antioxidant supplementation could inhibit oxidative DNA damage in lymphocytes, cure non-alcoholic fatty liver disease and alleviate chemotherapies' side effects in cancer patients [16-18]. The antioxidant content is usually determined with the oxygen radical absorbance capacity (ORAC) scale. However, Kadosh et al. [19] advised against antioxidant-rich diet such as black tea, cocoa and blueberries for people with a history of colorectal cancer because this could be risky for them. The United States Department of Agriculture estimated that men who live on an average of 2500 calories per day would require at least 11,000 ORAC units while women with 1800 calorie consumption per day would require at least 8,000 ORAC units [20].

4. HISTORICAL AND RECENT RESEARCH GLIMPSES ON THE EFFICACY OF ANTIOXIDANTS IN DISEASE THERAPY

The application of antioxidant drugs in human disease treatment can be categorized into three main classes. Firstly, the administration of endogenous antioxidants such as glutathione, superoxide dismutase, α-tocopherol and many more. Secondly, the application of synthetic antioxidants or chelating agents. Thirdly, administration of tissue repairing drugs with additional physiological advantages due to their antioxidant nature. For instance, captopril was found to function as an antioxidant in addition to being an angiotensin-converting enzyme inhibitor, although its antioxidant activity was found to be limited *In vivo* [21-23]. Antioxidants drugs have proven efficient in suppressing and treating both neurologic and nonneurologic disorders [24-25]. Several antioxidants such as vitamin A, C and E, N-acetylcysteine, selegiline, tirilazad, lutein, ebselen, lycopene, idebenone and selenium have been tested in oxidative stress-related diseases [9-10]. Some of these diseases are Alzheimer's diseases, amyotrophic lateral sclerosis (ALS) acute ischemic stroke, spinal cord injury, Parkinson's disease, dementia, Huntington's disease, epilepsy subarachnoid hemorrhage, cancer, cardiovascular diseases, and diabetics [26-27].

The efficacy of vitamin E a prototypic antioxidant has been widely studied in chronic neurodegenerative diseases and other oxidative stress-related diseases. The administration of vitamin E at 2000 IU/d delayed disease progression by about 7.4 months in Alzheimer disease during a treatment period of two years [28], while similar treatment with vitamin E, at 3000 IU/d for 12 months did not yield any positive result in Huntington disease [29]. Ogunmekan and Hwang [30] reported an improved epilepsy seizure control in 10 out of 12 children aged 5 to 18 years when they were treated with vitamin E at 4000 IU/d during three months while no improvement in seizure frequency was noticed in any of the 12 children given placebo in a randomized double-blind, placebo-controlled trial of vitamin E. Although treatment with vitamin E at 400 IU/d could not reduce the risk of cardiovascular disease in 14,641 male physicians not less than 50 years in the united states during ten years period of treatment, to years period of treatment, a prolonged supplementation of vitamin E (400 IU/d) decreased the risk of prostrate and total cancer cases amongst men [31-32]. Although a 21-aminosteroid antioxidant known as tirilazad mesylate prevents lipid peroxidation [33], it did not improve acute ischemic stroke at a dosage of 6mg/kg per day in 276 patients within 6hours of stroke onset as compared with 280 patients treated with placebo [34]. It reduced mortality at the same dosage when administered for 10 days in patients with subarachnoid hemorrhage [35]. Tirilazad mesylate at a dosage of 2.5mg/kg every 6 hours for two days preceded by methylprednisolone was as effective as uninterrupted 24-hours methylprednisolone [36] in patients with traumatic central nervous system injury. Recently, Cahill and Hall [37], called for the resurrection of this class of drugs to treat stroke in men. However, pyrrolopyrimidines a more recent group of compounds are equally effective but preferred to tirilazad mesylate due to their greater blood brain barrier penetrance [38-39].

N-acetylcysteine at 50 mg/kg per day for one year did not reduce mortality, muscle decline and disability in 55 patients with amyotrophic lateral sclerosis as compared with 56 patients given placebo [40]. A notable antioxidant known as ebselen (PZ51: 2-Phenyl-1,2-benzisoselena-zolin-3-(2H)-one) a glutathione peroxidase-mimic [41-42] considerably improved acute ischemic stroke in 300 patients when administered within

48 hours of stroke onset at 150 mg twice per day for 14 days [43].

In Parkinson's diseases [44], administering 10 mg of selegiline a neuroprotective antioxidant per day brought about nine months delay for the need of levodopa [45]. Moreover, Palhagen and co-workers [46] in a clinical trial confirmed that early treatment of Parkinson's disease with selegiline delayed the need for levodopa in 157 patients. Recently, Tabi and co-workers [47] also confirmed that selegiline is a potent antioxidant. Mercaptopropionylglycine (MPG), a thiol compound in several clinical studies has been found useful in the treatment of several oxidative stress-related diseases and its protective ability against perfusion injury after ischemia has been significant [48-49]. Allopurinol and oxypurinol, and xanthine oxidaze that can be injected or taken orally have been found effective against gastro-intestinal, cardiac and cerebral reoxygenation injury [50-51].

Over the years, several natural and synthetic drugs have been discovered and extensively studied for therapeutic applications. Some other antioxidants such as resveratrol, pyrrolidine dithio-carbamate, ascorbic acid, quercetin, ambroxol, catechins, iso-quercetin and 5,7,4-trihydroxy-8-methoxy flavones as superoxide anion scavengers are also used to inhibit the proliferation of influenza virus [52].

5. DRUG DESIGN

Drug is any substance, usually small organic molecule that exerts a therapeutic effect on a patient by activating or inhibiting a biomolecule's functions such as proteins or nucleic acid. Antioxidant drug design refers to the process of developing antioxidant medications based on the knowledge of the structures and functions of a biomolecular target [53]. The methodological approach in rational drug design (reverse pharmacology) eliminates the trial-and–error testing of hundreds of drug molecules on cultured cells or animals observed in the traditional method (forward pharmacology). It is based on the hypothesis that modulation of a specific druggable and disease-modifying biological target may have some therapeutic effects [54]; the shape and charge of a drug molecule must be complementary to the biological target with which they interact in order to be able to bind to it [55]. The antioxidant drug design involves the identification of a receptor that is relevant to an oxidative stress-mediated disease for which a drug is being designed,

elucidation of the structure and function of the receptor or enzyme and the designing of the antioxidant drug molecule that exhibits some therapeutic benefits when it interacts with the receptor or enzyme [54]. The significant types of drug design are currently ligand-based and structure–based relying on the knowledge of the binding molecule and the three dimensional structure of the biological target [56]. The ligand-based design also known as indirect drug design is dependent on the knowledge of other molecules that bind to specific biological targets [57]. The structure-based design referred to as direct drug design is based on three current methods, namely; virtual screening, *de novo* design of ligands and optimization of known ligands [58]. However, computer-aided drug design that enables the prediction of binding affinity before a compound is synthesized is usually utilized at various stages of drug design such as hit identification by virtual screening, hit and lead optimization of affinity/selectivity and lead optimization of other relevant pharmacological properties [59-60]. Moreover, other properties such as metabolic half–life, bioavailability and toxicity must be ascertained before a ligand is considered an efficacious and safe antioxidant drug [61].

Concerning natural antioxidant drugs, the earlier limitations experienced, such as the labor-intensive purification process, lack of dereplication, and difficulty in modifying structurally complex natural products have been overcome by technological advancements and the discovery of new methods [62]. The recent advancement in sourcing, screening, synthesis, combinatorial biosynthesis, structure elucidation and microbial genomics of natural products have revolutionized natural antioxidant drug discovery [62]. The abundance of secondary metabolites of plants and microbes, and the advancement in genomics, cellular biology and molecular biology have also increased the number of hits, leads and targets thereby reducing the natural antioxidant drugs discovery timelines [62]. It has been observed that natural products are essential sources for novel antioxidant drugs and their secondary metabolites exhibit better drug-likeness and biological friendliness than synthetic molecules thereby making them good candidates for antioxidant drug development [63-64].

6. RATIONAL DRUG DESIGN FOR ANTIOXIDANTS

Rational drug design of novel antioxidants in addition to a selection from natural products and

synthetic compounds have become special areas of research interest. In recent times, there has been a concentrated focus on the rational design of novel antioxidants due to several advantages attached to it. This method of drug design involves two types of strategies namely; (1) modification of the existing antioxidants using QSAR for improved potency according to specific demands, (2) designing an utterly new antioxidant from a novel structure, popularly known as *de novo* design.

7. QUANTITATIVE STRUCTURE-ACTIVITY RELATIONSHIP (QSAR) FOR ANTIOXIDANTS

The quantitative structure-activity relationship (QSAR) for antioxidants involves the correlation of the chemical structures with an antioxidant activity using statistical approaches [65]. Presently, QSAR models are employed to predict and classify antioxidant activities of several compounds, thereby making it a necessary tool in the pharmaceutical industry for lead discovery and optimization to lead development of antioxidant drugs [66-67]. It is usually employed early in antioxidant drug design to screen and eliminate compounds with low toxicity profile and compounds that lack drug-like properties. However, a quantitative structure-property relationship (QSPR) study is often added to envisage the various physical and chemical properties of the compounds under consideration [68].

There are three essential steps involved in quantitative structure-activity relationship (QSAR) study for antioxidant drug design namely; (1) collection or design of a training set of chemicals, (2) selection of descriptors that can correlate chemical structure with antioxidant activity, and (3) application of statistical methods that relate changes in structure to changes in antioxidant activities. Statistical correlation of the experimental activity with structural factors and representing them by numerical values has over the years been accepted as the standard method to obtain QSAR [69]. There are two basic physicochemical parameters, namely; homolytic bond dissociation enthalpy (HBDE) and ionization potential (IP), that are essentially required in the elucidation of the quantitative structure-activity relationship (QSAR) of antioxidants [70]. This is because bond dissociation enthalpy (BDE) and ionization potential (IP) represent the radical-scavenging activity to a great extent and therefore

characterize the antioxidant activity of a molecule. The role of BDE in the determination of QSAR equation underscores the importance of H-atom transfer in radical-scavenging [70]. The value of IP is required to characterize the electron-donating ability of antioxidants [70]. The QASR study avails an easy, inexpensive and non-destructive method of identifying and designing new antioxidants before synthesis. Chemical structural features known as molecular descriptors are used for heterogeneous and homogeneous groups and all of them have a correlation with antioxidant activity. It was observed that when classical two-dimensional (2-D) QSAR study was compared with three-dimensional (3-D) QSAR method particularly comparative molecular field analysis (CoMFA), 2-D QSAR result was better than that of 3-D QSAR for antioxidant compounds [71]. In recent times, flavonoids have become a rich source for modelling leads with targeted pharmacological properties due to their structural diversity and multiple activities. The disparity in their physiological activities is attributed to different substituent groups' presence on the carbon atom of the fundamental flavonoid structure and the difference in lipid solubility [72].

Ahmad and co-workers [73] recently developed a QSAR model that was used to describe the relationship between some flavonoids obtained from Chinese herbs and their corresponding antioxidant activities. They confirmed the QSAR model's significance using leave-one-out cross-validation, external validation, and Y-randomisation/scrambling techniques in which two–dimensional (2D) block of descriptors PW5 and JG14 were used. It was observed that the low value of specific topological indices of molecules (PW5) and the high value of the mean topological charge index (JG14) increased and enhanced the flavonoids' antioxidant activity value. It has been confirmed that the antioxidant activity of a flavonoid depends on its chemical structure and it is influenced by the number and position of hydroxyl groups on the B and A rings and the degree of conjugation experienced between the B and C rings (Fig. 1) [74-75].

The QSAR study of flavonoids for antioxidant activity appears exciting. The structural requirements for efficient radical-scavenging and antioxidant potentials of flavonoids is governed by Bors' criteria [76] as follows: (a) an *orth-*dihydroxy (catechol: 3,4-diOH) structure in ring B confers much stability to flavonoid phenoxyl radical through hydrogen bonding or

delocalization of election; (b) the (C2-C3), 2,3-double bond in conjugation with a 4-oxo functional group (1,4-pyrone) in ring C which is responsible for the coplanarity of the hetero ring and radical stabilization through the delocalization of electron over the three-ring system; (c) availability of both 3- and 5-hydroxyl groups that ensure effective radical scavenging and absorption. Moreover, when the *O*-dihydroxyl structure is not available in ring B, there is compensation by the hydroxyl substituent in a catechol structure on ring A which will largely determine the antiradical activity of the flavonoids [77-79]. Van Acker and

co-workers [80] reported that the basic flavonoid skeleton does not seem to be essential for efficient antioxidant activity but becomes necessary only in the absence of the catechol moiety. The antioxidant properties of flavonoids can be decreased by removing the 3-OH group or blocking the OH group at the C-3 position.

The catechol enhances the radical-scavenging activity of flavonoids and phenolics and this accounts for quercetin being much more active than morin though the only difference between them is the OH positions in ring B (Fig. 2) [81-82].
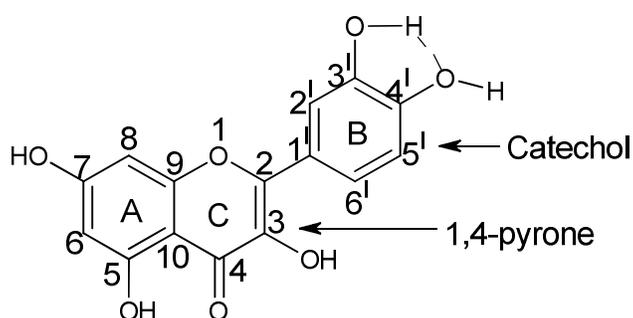

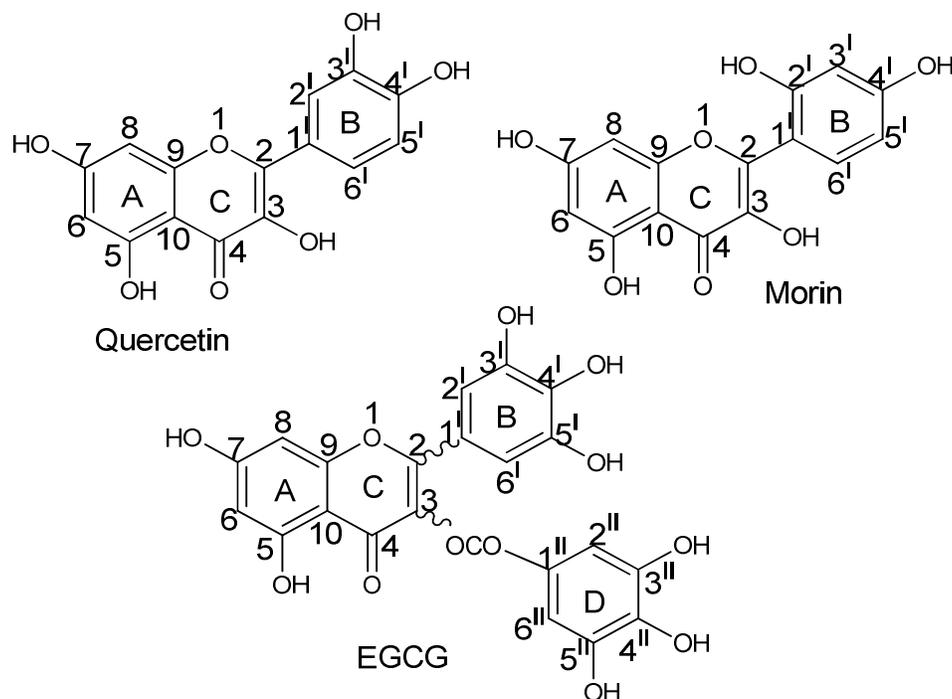**Fig. 1. Flavonoid antioxidant structural factors [72]**

Fig. 2. Molecular structure of quercetin, morin and EGCG [72]

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Moreover, pyrogallol structure also raises the antioxidant potential of compounds therefore catechol and pyrogallol are essential pharmacophore of antioxidants [82-84]. In addition to catechol pyrogallol and 1,4-pyrone, the effect of 3,5-OH on the bond dissociation enthalpies and ionization potentials are required to elucidate the QSARs of antioxidant flavonoids [72] fully. The antioxidant potential of pyrogallol structure is seen in the fact that amongst all the green tea polyphenols, (-)-epigallocatechin gallate (EGCG) (Fig. 3) is the most potent antioxidant [85]. Flavones having both 7-OH substitution and catechol or pyrogallol moiety on the ring B was recognized as the strongest inhibitors of xanthine oxidase [86].
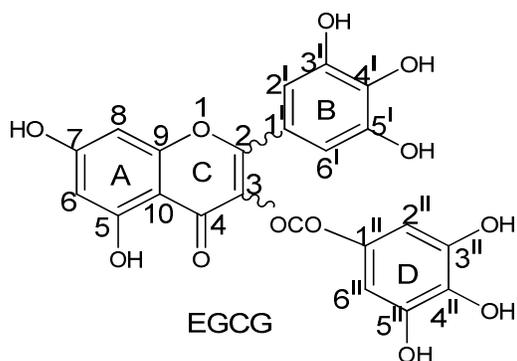
Fig. 3. Structure of (-)- epigallocatechin gallate (EGCG) [85]

It was recently proposed that the fused heterocyclic ring is responsible for the great antioxidant activities of tocopherols. The π-type lone pair of oxygen in the fused heterocyclic ring perpendicular to the aromatic ring overlaps with the π-system in the singly occupied molecular orbital (SOMO) of the tocopherol derived radical [87]. The overlap helps to stabilize the radical by resonance and this accounts for higher activity in α-tocopherol when compared with tetramethyl-*p*-methoxy–phenol (TMMP). Furthermore, this can be attributed to the steric hindrance observed between the *m*-methyl groups and *p*-methoxy group; the TMMP radical cannot be stabilized since the π-type lone pair orbital of oxygen in the TMMP lies on the plane of the aromatic ring. The comparative study of the radical scavenging rate constants of α, ß, Ƴ and δ-tocopherol revealed that an increase in the number of methyl groups resulted in an increase in the antioxidant activity of tocopherols and this is because electron-donating groups help to stabilize phenoxy radicals (Fig. 4) [88].

On the other hand, an increase in the OH-BDEs of α-, ß-, Ƴ- and δ- tocopherol is observed with a decrease of the methyl groups on the phenyl rings. The five-member analogy of α-tocopherol was more active than the six-member analog because the five-membered ring analog is more planar and enable ʎ-type lone pairs that exert a stabilizing effect on the radical. This discovery is the basis on which 2,3-dihydro-5-hydroxy-2,2–diphenyl-4,6-ditertbutyl benzofuran was designed and improved [88]. Zhang [72] enlisted the significant improvements as follows, (a) reduction of OH-BDE and hindrance of the attack of the free radical of BO-653 on other biomolecular targets as a result of the substitution of two moieties of *O*-tertbutyl; (b) improvement of cellular mobility of BO-653 in membranes and lipoprotein and (c) an opened-7-position that enables peroxy radical addition to the phenoxy radical of BO-653 (Fig. 5).

Mukai and co-workers with the help of QSAR study, reported the relative antioxidant activities of α-tocopherol and abiquinol-10 based on their Ks values and concentration in several tissues and serum [89]. Baj et al. [87] in a new approach to QSAR study of α-tocopherol aligned with Burton and Ingold concept that the stereo electronic effects exerted by an oxygen atom in dihydropyranyl ring were responsible for the high antioxidant activity of α-tocopherol. They assessed the influence of the O1 atom on the antioxidant activity of chroman-6-OLS through quantitative estimation [87-88].

The antioxidant activities of 22 pinoline derivatives (1,2,3,4-tetrahydro-ß-carbolines) were predicted using two-dimensional quantitative structure-activity relationships (2-D QSARs) analysis with the aid of a predictive model. The structural insight into the main features responsible for the strong antioxidant activity of compounds derived from pinoline scaffold was given before they were synthesized. It was observed that the antioxidant activity of compounds could be governed by other parameters such as molecular properties, topological properties and functional groups [90].

Filipovic et al. [91] reported the antioxidant activities of 21 selected hydroxybenzoic acids and simple phenols using QSAR analysis. Based on this study, it was recommended that fair antiradical QSAR models would facilitate the design of antioxidants with improved antiradical potency. The QSAR analysis compounds by

Hoelz and co-workers [92] showed that the best phenolic antioxidants are those containing electron donor groups directly attached to the aromatic ring. The study revealed that the disparity in the solubility of the aqueous and hydrophobic phases does not affect the antioxidant activity of series of phenolic compounds [92]. The QSAR study of series of synthetic chromone derivatives showed that the electronegative group on benzoyl ring and the electropositive group on phenyl ring account for their antioxidant activity because these groups enable radical stabilization throughout the chromone nucleus. It was observed that bulky substituent groups near position five and chromone carbonyl were disfavoured. The radical delocalization was affected by steric hindrance interference with the planarity between ring A and the carbonyl group of the chromone nucleus (Fig. 6) [93].

Recently, Chen et al [94], reported a QSAR study on 91 antioxidant tripeptides and concluded that established QSAR models are required to identify and screen novel antioxidant tripeptides with high antioxidant activity. It was recommended that a thorough quantitative structure-activity relationship (QSARs) analysis for enzyme inhibitors should be conducted before a rational drug design for antioxidant drugs through an integrating strategy is initiated [72].
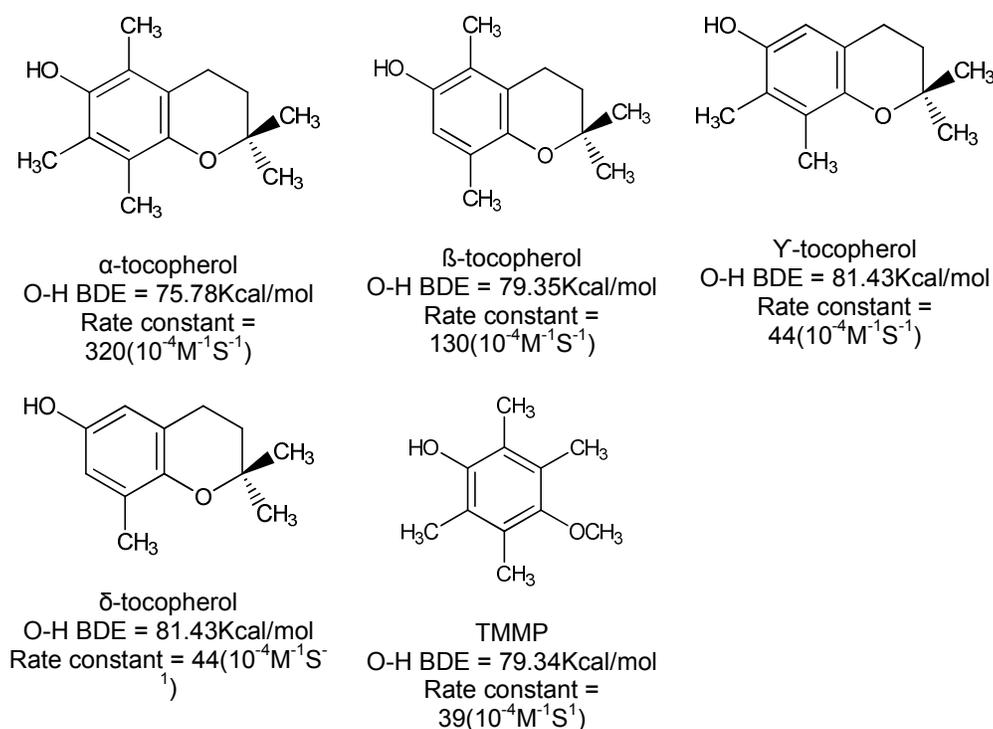

α-tocopherol
O-H BDE = 75.78Kcal/mol
Rate constant =
$320(10^{-4}M^{-1}S^{-1})$

ß-tocopherol
O-H BDE = 79.35Kcal/mol
Rate constant =
$130(10^{-4}M^{-1}S^{-1})$

Y-tocopherol
O-H BDE = 81.43Kcal/mol
Rate constant =
$44(10^{-4}M^{-1}S^{-1})$

δ-tocopherol
O-H BDE = 81.43Kcal/mol
Rate constant = $44(10^{-4}M^{-1}S^{-1})$

TMMP
O-H BDE = 79.34Kcal/mol
Rate constant =
$39(10^{-4}M^{-1}S^{1})$

Fig. 4. Structures, O-H BDE and rate constants of tocopherols and TMMP [88]
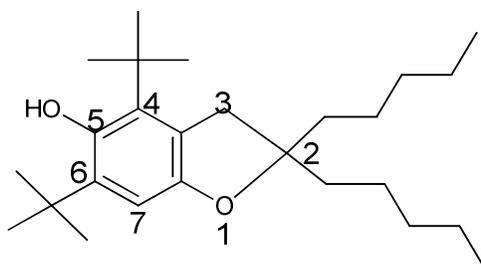

Fig. 5. The structure of BO-653 [72]

These strategies were carried out on the basis of the structural requirements of an effective antioxidant which could be derived from quantitative and qualitative SARs of antioxidants [95]. QSAR studies of antioxidants showed that excellent radical-scavenging antioxidants must possess three essential features. (i) The X(O,S,N,C)-H bond dissociation enthalpy (BDE) or ionization potential (IP) should be suitable. It was observed that low BDE and IP favour direct radical-scavenging activity in polar or non-polar solvents. Polar solvents and very low ionization potential enhance pro-oxidant danger due to direct electron transfer to oxygen [96-98]. (ii) The solubility must be appropriate in the applied environments. It was pointed out that hydrophobic antioxidants perform better in an emulsion system while hydrophilic antioxidant exhibit better activity in bulk lipids [99-100]. Hydrophobicity is preferred to hydrophilicity due to the heterogeneous nature of biological and chemical systems and some degree of lipophilicity is required for antioxidants to penetrate the bio-membrane. (iii) The toxicity profile of antioxidants and their metabolites in addition to antioxidant derived radicals should be at the barest minimum [101-102]. These prerequisites should be considered for a successful design of novel antioxidants of high activity and low toxicity.

## 8. *De novo* DESIGN OF ANTIOXIDANT DRUGS

This method of drug design employs two successful strategies. (1) Good features of two or more antioxidants are assembled into a single molecule. (2) New structures are discovered by computer–aided methodologies [95]. Several illustrations are given below.

The combination of an antioxidant moiety of α-tocopherol and uric acid yielded hydroxylphenylurea a lead structure that exhibited about ten times higher antioxidant activity than individual α-tocopherol or uric acid moiety (Fig. 7) [103].

The better stabilization of the odd electron by the –OCH$_3$ and urea functionalities accounts for the higher radical-scavenging activity observed in hydroxyphenyl urea [103]. Similarly, the design of FeAOX-6, an antioxidant of higher activity was achieved by the combination of α tocopherol and lycopene (Fig. 8) [104].
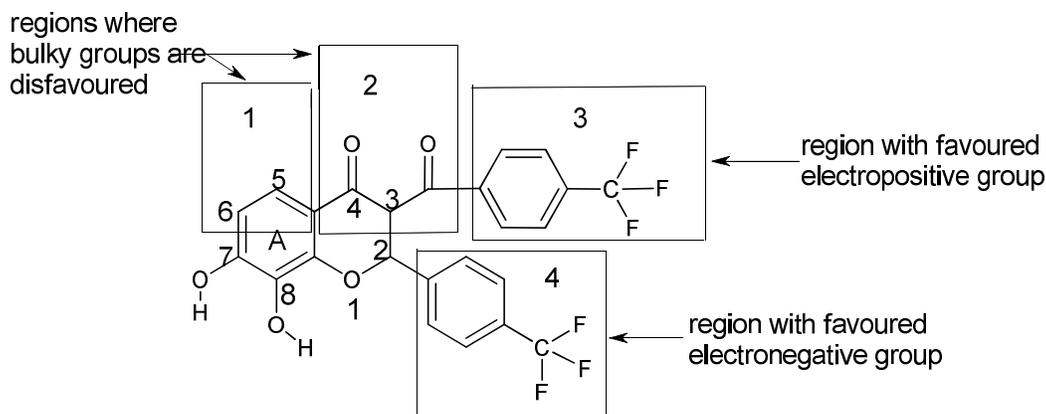
Fig. 6. Mapping the best MFA model and interaction points for synthetic antioxidant chromone derivatives [93]
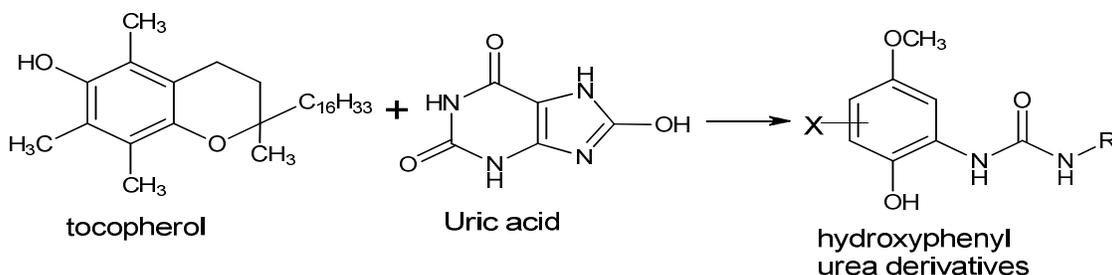

Fig. 7. Synthesis of hydroxyphenylurea [103]
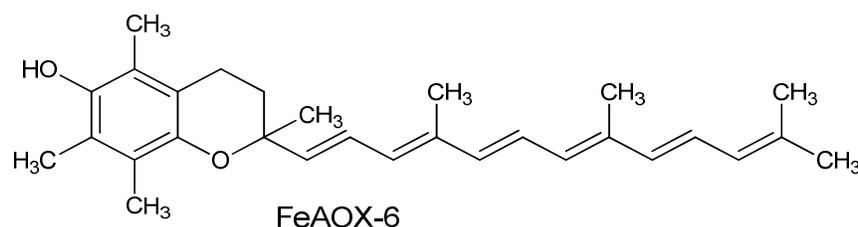
Fig. 8. FeAOX-6 structure

For computer-aided antioxidant drug design, there is a need to find a promising lead with appropriate BDE and IP, proper solubility and low toxicity profile. A "design window concept" proposed that the BDE of a lead should be higher than BDE of ascorbate ion (±65.5kcal/mol) and lower than that of α-tocopherol (±77kcal/mol). This strategy guarantees a successful design of antioxidants more active than α-tocopherol which can also be regenerated by ascorbate ion. It is believed that the first antioxidant lead successfully designed by computer-aided methodology was 5-hydroxypyrimidine (Fig. 9). Its O-H BDE was found to be comparable with phenol and its ionization potential (IP) at 24kcal/mol is higher than that of phenol [105-106].
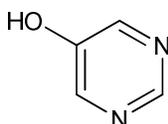
Fig. 9. 5-hydroxypyrimidine

Based on the design window concept and quantum chemical calculations, several analogs such as 2,3-naphthalenediol, 3-pyridinol, *N-tert*butyl-*N*-hydroxylaminophenyl derivatives and 1,4-bis(benzimidazole-2-yl-methyl)-1,4,7-triazacyclone an SOD mimetic was designed as potent antioxidant leads [72]. Using a similar method, a planar catechin analog was successfully designed and synthesized. It exhibited less toxicity and higher antioxidant activity than catechin against galvinoxyl radical in deaerated MeCN solution (Fig. 10i) [107-108]. Karmaker et al. [109] reported the design of a series of benzimidazoles with nitro substituents which exhibited higher antioxidant than BHT. Watanabe and co-workers reported a rational design and clinical trials of novel antioxidant edaravone (3-methyl-1-phenyl-2- pyrazolin-5-one) (Fig. 10ii) used in the treatment of acute cerebral infarction [110].Martincic et al. [111]

reported a rational design of some novel antioxidants on the basis of pulvinic acid and coumarine derivatives (Fig. 10iii) based on QSAR and pharmacophore models. Egbujor et al [112] reported a design and synthesis of α-amino acid-based sulphonamide derivative, 3-hydoxy-2-[(phenylsulfonyl)amino]propanoic acid (Fig. 10iv) having antioxidant activity comparable with ascorbic acid. Serine was utilized in this design and several amino acids were also explored [113]. Several sulphonamide analogs have been identified as antioxidant leads [114-120]. Recently, Wang et al. [121] reported the design of chalcone analog with high antioxidant activity known as (E)-1-(3,4-dihydroxyphenyl)-3-(2,5-dimethoxyphenyl)prop-2-en-1-one (Fig. 10v) and several antioxidant chalcones have been reported [122]. This novel compound conferred cytoprotection of H_2O_2-induced oxidative damage in PCl2 cells by simultaneously scavenging free radicals and activating NRF2/ARE. It also helped against ischemia/reperfusion-related brain damage in animals [121].

9. DESIGN OF MULTIFUNCTIONAL ANTIOXIDANTS

Bifunctional and multipotent antioxidants seem to be more effective than single-functional antioxidants in combating diseases such as Parkinson disease, Alzheimer's disease, amyotrophic lateral sclerosis, and many more [123-124]. The incorporation of the antioxidant's active center with other pharmacophores paves a new way for the rational design of novel drugs. The most recent rational drug design strategy for bifunctional and multipotent antioxidants involves connecting an antioxidant group and other pharmacophores using a linker. In addition to the combination of several antioxidant properties such as radical–scavenging and metal-chelating abilities, other pharmacophores could be incorporated to afford hybrid compounds with multiple pharmacological activities through a single structure [72,123]. Several antioxidants obtained by the replacement of the furoyl moiety of prazosin, an α-adrenoreceptor antagonist

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possessing lipoyl fragment of lipoic acid. Its lower homologs or 1,4-naphthoquinone exhibited potent α-adrenoreceptor antagonism, and anti-proliferative activities (Fig. 11) [125].

Antioxidants with acetylcholinesterase (AChE) inhibitory activity were reported. Lipocrine (Fig. 12i) a multipotent antioxidant with acetylcholinesterase (AChE) inhibitory ability was designed by the incorporation of lipoic acid into a tacrine structure [126]. Similarly, a pineal neurohormone and a preventive antioxidant was produced by the coupling of tacrine to melatonin (Fig. 12ii) [127]. The antioxidant and AChE activities of lipocirne and the later were higher than that of the prototypic molecules constituting the hybrid structure [126-127]. Adewusi et al [128] reported some excellent antioxidant and acetylcholinesterase inhibitory activities of *C. mimosociles, B. salviifolia* and *S. brachypetala*, selected Southern African medicinal plants. Recently, Reza et al [129] reported that *Elatostema papillosum* has excellent cholinergic inhibitory and antioxidant activities. Multipotent antioxidants with cholinesterase inhibitory activities are recommended for the treatment of Alzheimer's disease due to its complex pathology [128-129].

Antioxidant with anti-inflammatory activities was designed by combining naproxen or indomethacin (nonsteroidal anti-inflammatory drugs) with cystemain or cystein ethylester (antioxidants) into a proline-based framework (Fig. 13i) [130]. Yehye et al [131] reported a rational design of multipotent Schiff-base-1,2,4-triazole antioxidant bearing butylated hydroxytoluene moiety (Fig. 13ii) by attaching Schiff base 1,2,4-trazoles to the oxygen derived free radical scavenging moiety, butylated hydroxytoluene (BHT). It was observed that the Schff base-1,2,4-triazoles improved the antioxidant capacity of BHT. Several antioxidant morpholine derivatives with multifunctional activities were previously designed against atherosclerosis and diabetes [132-133]. Recently, Matralis and Kourounakis [133], based on a rational drug design accompanied by QSAR analysis reported a novel multifunctional morpholine derivative (Fig. 13iii) with improved antioxidant and antihyperlipidemic activity.
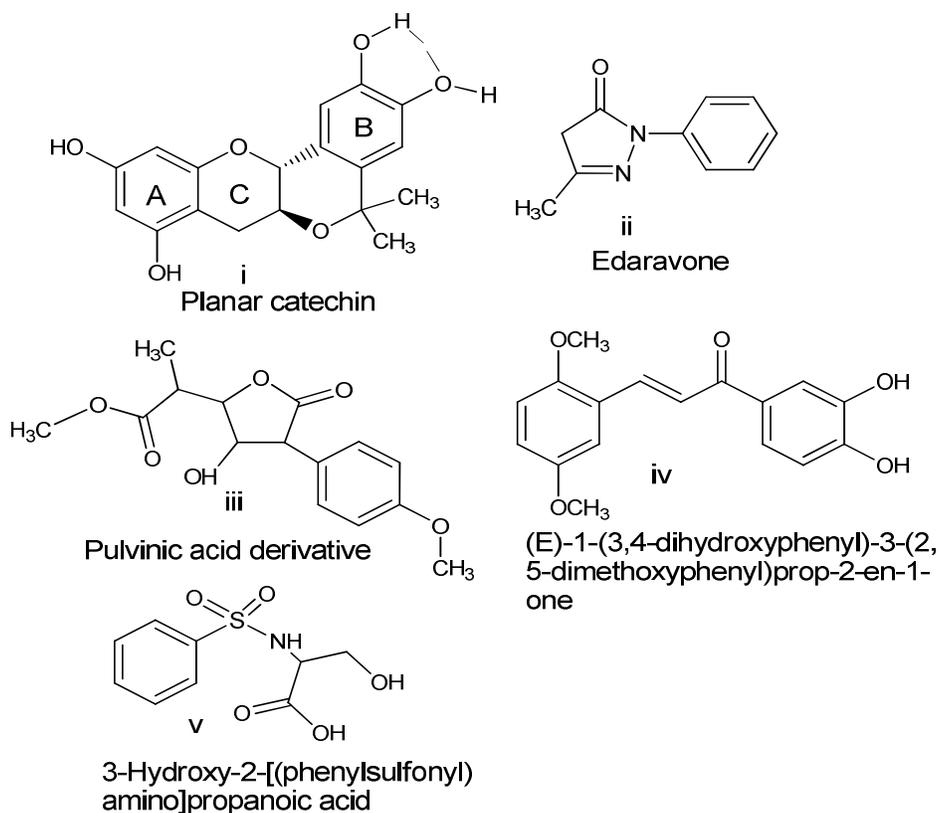

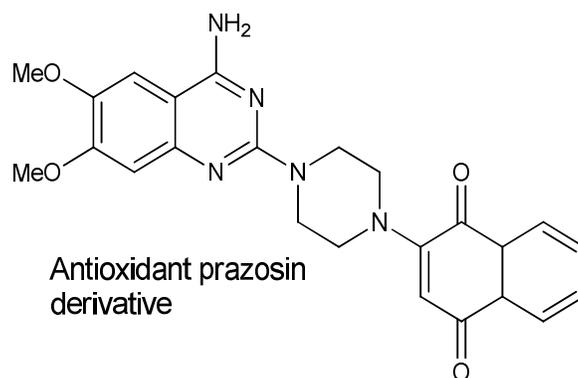**Fig. 10. Structures of recently designed antioxidants**

Planar catechin — i

Edaravone — ii

Pulvinic acid derivative — iii

(E)-1-(3,4-dihydroxyphenyl)-3-(2, 5-dimethoxyphenyl)prop-2-en-1-one — iv

3-Hydroxy-2-[(phenylsulfonyl) amino]propanoic acid — v

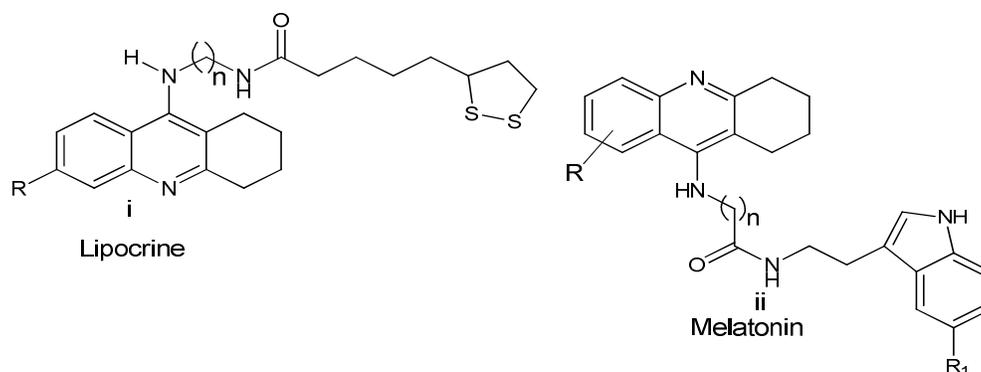**Fig. 11. Active antioxidant prazosin derivative [125]**

Fig. 12. Designed multifunctional antioxidants with acetylcholinestrase (AChE) inhibitory activities

It has been reported that multifunctional antioxidants with Ca^{2+} channel blocking pharmacophores could improve ischemic heart disease due to the fact that cardiomyocyte damage and heart tissue damage are attributed to oxidative stress and Ca^{2+} overload [134]. Several years ago, antioxidant/Ca^{2+} antagonist (thiazolidinone derivative CP-060) (Fig. 14i) was designed and synthesized [134]. Recently, Santa-Helena et al. [135] reported novel calcium channel blocker, dihydropyridine derivative (Fig. 14ii) that showed better inhibition of lipid peroxidation than original nifedipine drug. This nifedipine analog possesses two molecules of oleic acid and chlorine in the position 2

Although some significant advances have been made in the rational design of multipotent/multifunctional synthetic antioxidants, the structural characteristics of their conjugates are different from those of natural origin. The framework of the natural product is seamless and the pharmacophores for different targets are thoroughly merged [72,136]. This could be responsible for their lower toxicity and easy

development. Owing to the fact that quercetin is a typical multipotent antioxidant possessing the significant radical-scavenging ability and inhibitory activity against extra 10 separate enzymes, it is therefore recommended as a prototype for detailed assessment and elucidation of some elements of natural antioxidant. In addition to the radical-scavenging ability revealed by QSARs as discussed above, quercetin analogues are also enzyme inhibitors [136]. The diverse pharmacological properties of quercetin is due to the functional group substitutions of flavonol molecule [137]. Recently, Simanjuntak et al. [138] reported a structure based drug design of a quercetin derivative against high mobility group box 1 (HMGBI). It was observed that in addition to radical-scavenging ability, quercetin, 3-sodium sulphate (Fig. 15i) could act as an anticancer agent. The polyphenol curcumin (diferulolmethane) derived from *Curcuma longa* is an established antioxidant. In recent times, interest has been shifted to the rational design of antioxidant curcumin nanoparticles, several researchers have recently reported some

improved antioxidant, anti-cancer and antimicrobial activity of curcumin nanoparticules when compared with original curcumin [139-140]. Myricetin is an excellent multifunctional antioxidant that has been extensively studied. Barzegar [141] observed that intracellular ROS inactivation, and ferric ion reduction are important properties of myricetin. Ruan et al. [142] reported a rational design of novel myricetin derivatives bearing amide, thioether

and 1,3,4-thiadiazole functionalities (Fig. 15ii). It was reported that apart from the antioxidant activities, these myricetin derivatives exhibited good antibacterial activities [142]. Other multifunctional natural antioxidants such as (-)-Epicatechin-3-gallate, gossypetin, rutin, Quercitrin, and isoquercitrin that can scavenge free radicals and sequester metal ions are also designed based on the knowledge of the QSAR analysis of quercetin [72,124].
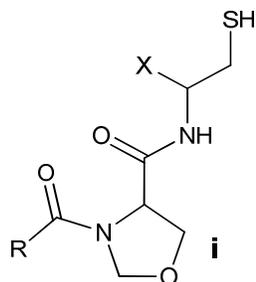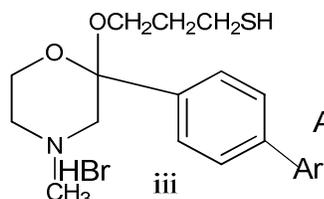
R = indomethacin residue or naproxen residue

Bifunctional antioxidant with anti-inflammatory activity

ii
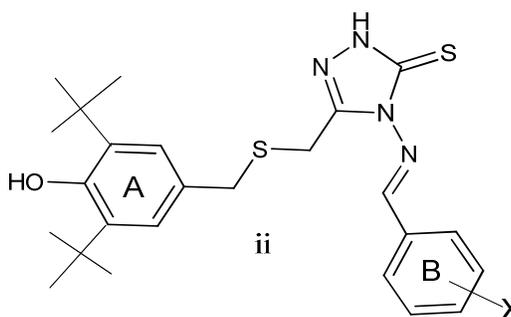
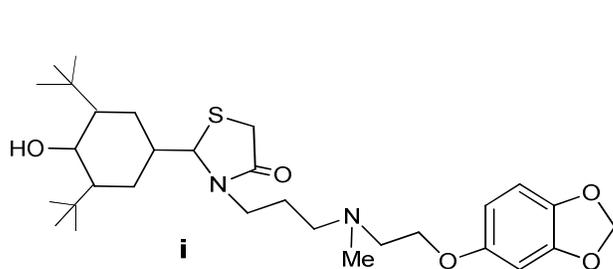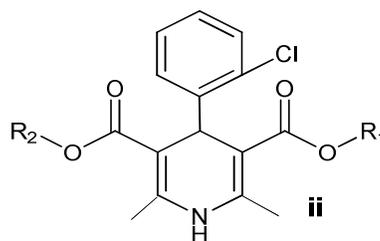Multipotent antioxidant with improved antioxidant capacity of BHT

Ar = 2-naphthalene

Bifunctional morpholine derivatives antioxidant with antihyperlipidemic activity

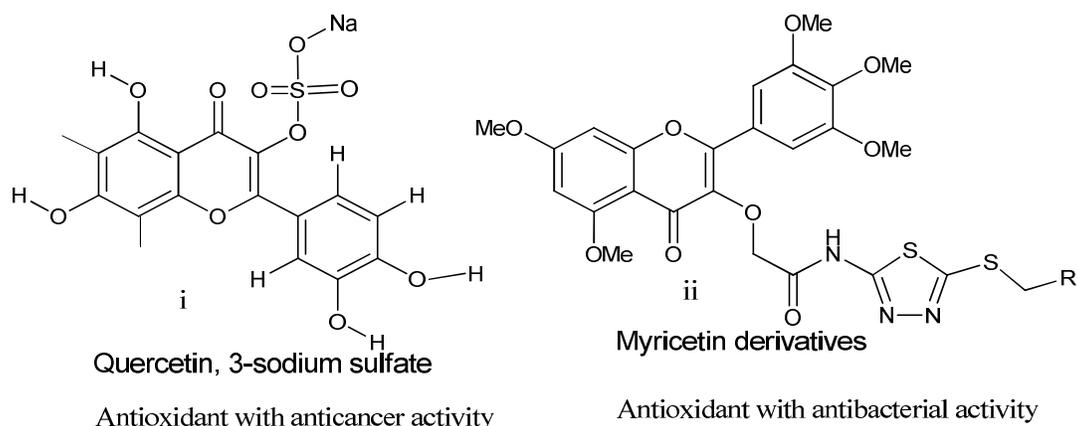**Fig. 13. Designed multifunctional antioxidants with anti-inflammatory, antihyperlipidemic activities**

CP-060

Dihydropyridine derivative

Fig. 14. Designed multipotent antioxidants with Ca^{2+} channel blocking ability

i

Quercetin, 3-sodium sulfate

Antioxidant with anticancer activity

ii

Myricetin derivatives

Antioxidant with antibacterial activity

Fig. 15. Designed multipotent natural antioxidants

10. CONCLUSION

The therapeutic effects of antioxidant drugs against oxidative stress-mediated diseases such as cancer, neurodegenerative diseases, cardiovascular diseases and many other prevalent diseases have been established over the years. Based on this fact, concerted efforts have been engaged in frontier researches for the design of antioxidant drugs with improved potency for the last few decades. This review therefore provides a historical and up-to-date collection of research briefs on antioxidant drug design reported in different journals and articles into one piece. Useful insights on future researches on antioxidant drug discovery and design were also projected herein. This work should provide relevant information on antioxidant drug design, increase readership and stimulate interest for the discovery and development of more potent antioxidant drugs.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

ACKNOLEDGEMENT

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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