ELSEVIER

Multipotent antioxidants: from screening to design

Hong-Yu Zhang, Da-Peng Yang and Guang-Yan Tang

Shandong Provincial Research Center for Bioinformatic Engineering and Technique, Center for Advanced Study, Shandong University of Technology, Zibo 255049, P.R. China

Free-radicals play an important role in the pathogenesis of many diseases, accounting for continuing interest in the identification and development of novel antioxidants that prevent radical-induced damage. To develop more-powerful weapons that address complex diseases in which free-radicals might be significant, but not exclusive drivers, antioxidants that also have other pharmacological effects are desired. To obtain multipotent antioxidants, one can screen drug collections and/or natural-product libraries, or couple an antioxidant group with other pharmacophores. It is interesting to note that most rationally designed multifunctional antioxidants are structurally different from their naturally occurring counterparts. Therefore, nature's design strategy provides important clues as to how the design concept for multipotent antioxidants can be improved.

Because most diseases are induced by more than one pathogenetic factor, the current drug discovery paradigm is shifting from addressing single molecular targets to multiple ones [1–7]. As a result, more and more attention is being paid to finding multipotent agents that can surpass the therapeutic effects of selective drugs [1–6]. Because free-radicals are implicated in the initiation and progression of many diseases, especially neurodegenerative diseases [8–10], in recent years a great deal of effort has been devoted to finding multipotent antioxidants (Box 1); in an attempt to combine radical-scavenging (and/or radical-generation-preventing) activity and enzyme-inhibiting potential into a single structure. Although cocktails of antioxidants and other drugs could be an alternative approach to address multiple targets (including radicals), multipotent antioxidants could have a reduced liability with respect to drug–drug interactions and, hence, more-predictable pharmacokinetic behaviors [3,4].

Multifunctional antioxidants can be obtained by two approaches (i.e. screening in compound or drug libraries, or rational design by the combination of pharmacophores). The screening approach is dependent, to an extent, upon serendipitous findings in addition to basic biological and chemical research on synthetic compounds and natural products. The other method attempts to design and synthesize hybrid molecules, linking an antioxidant group to one or more enzyme-inhibitor pharmacophore. Many successful examples have been demonstrated using both paradigms.

Screening of multipotent antioxidants

The belief that multipotent antioxidants can be found from compound or drug collections arises from the fact that some known natural products and synthetic drugs are indeed multifunctional antioxidants. For instance, ascorbic acid and tocopherols are not solely very efficient chain-breaking antioxidants, they are also essential vitamins. In addition, 1,4-dihydropyridine derivatives possess dual activity as preventive antioxidants and L-type calcium-channel blockers [11].

In the past several years, many multipotent antioxidants have been identified, most of which have efficacy in the treatment of neurodegenerative diseases [e.g. Alzheimer's disease (AD)] in which multiple pathogenetic factors, such as free radicals, metal ions (e.g. Cu^{2+}, Zn^{2+}, Fe^{3+}), aggregated amyloid-β peptide (Aβ) and tau protein, acetylcholinesterase (AChE), and monoamine oxidase (MAO), are implicated. A good example of an AD-modifying multipotent antioxidant is curcumin (Figure 1). First, curcumin is a radical scavenger and it is this activity that has attracted significant investigation. According to the statistical analysis of

Corresponding author: Zhang, H.-Y. (zhanghy@sdut.edu.cn)

1359-6446/06/$ - see front matter doi:10.1016/j.drudis.2006.06.007

BOX 1

What are antioxidants and what are multipotent antioxidants?

Antioxidants are compounds that can prevent biological and chemical substances from radical-induced oxidation damage. Because radical oxidation of substrates occurs through a chain reaction that includes three stages (i.e. initiation, propagation and termination), antioxidants show their effects through various mechanisms. For instance, they can inhibit pro-oxidant enzymes that generate radicals (as enzyme inhibitors, targeting the initiation of the chain reaction), chelate transition-metal ions that catalyze the generation of radicals (as metal chelators, targeting the initiation of the chain reaction) or neutralize radicals (as radical scavengers, targeting the propagation of the chain reaction). The first two types of antioxidant prevent the generation of radicals and, thus, reduce the danger of radicals indirectly. These are called preventive antioxidants. The third group of antioxidants scavenges radicals directly and they are, therefore, referred to as chain-breaking antioxidants. In addition, some antioxidants exert their effects by raising the levels of endogenous antioxidant defenses *in vivo*, for example upregulating expression of the genes encoding superoxide dismutase, catalase and/or glutathione peroxidase. Because these antioxidant mechanisms are not mutually exclusive, multiple antioxidant properties can be found in a single compound, which would therefore be referred to as a multipotent antioxidant. However, in a broader sense, multipotent antioxidants are defined as compounds with other pharmacological effects, as well as antioxidant activity. This type of multipotent antioxidant is of great interest for the treatment of complex diseases, for example Alzheimer's disease, in which diverse pathogenetic factors (other than free-radicals and metal ions) are implicated, and this group is, therefore, given special attention in this review.

Litwinienko and Ingold [12], 248 papers containing the word-pair 'curcumin and antioxidant' appeared in the period 2000–2002. Second, this molecule has been shown to possess a range of pharmacological properties, including anti-inflammatory, anticoagulant and anticarcinogenesis activities, among others [13–15]. More recently, curcumin was identified as an efficient Aβ-aggregation blocker (IC_{50} <1 μM) [16,17] and a good metal (Cu^{2+}) chelator [18–20]. The integration of radical scavenging, metal-ion chelating, Aβ-aggregation inhibition and anti-inflammatory properties make curcumin a very promising multipotent ligand for the treatment of AD [20]. This is supported to some extent by epidemiologic investigations that show that in rural India AD prevalence is only 1% in people over the age of 65, where turmeric (the main source of curcumin) is commonly used in food [21] (by comparison, the prevalence of AD in the same age-group from a multiethnic community from East Boston, Massachusetts, USA is >10%) [22]. In addition to curcumin, flavonoids such as quercetin, gossypetin, myricetin, (−)-epicatechin-3-gallate, quercitrin, isoquercitrin and rutin (Figure 1) are also multifunctional antioxidants that might be useful in the treatment of AD. They have long been known to be excellent radical scavengers, endowed with strong metal-chelating ability [23]. Moreover, some of them can block Aβ or tau protein aggregation with IC_{50}s <10 μM [24–26], and some can inhibit MAO-B with IC_{50}s of ~10 μM [27]. In addition, xanthones, a special class of flavonoids, were also identified as efficient radical scavengers [28,29], MAO (including isoenzymes A and B) inhibitors [30,31] and potential AChE inhibitors [31]. Therefore, it is highly probable that multipotent antioxidants from compound collections, especially natural-product libraries, will be found.

To get some insight into the distribution profiles of multipotent antioxidants in natural-product and drug libraries, we searched the traditional Chinese medicine database (TCMD) [32] and the comprehensive medicinal chemistry (CMC) database [33]. The former database records 10,458 natural products extracted from >4000 Chinese medicinal plants, and the latter database contains 8659 drugs.

Although examining the CMC database unearthed only 16 antioxidants, and seven of them possessed pharmacological effects other than antioxidant activity (Table 1, supplementary material), the searches in TCMD returned 88 molecules (i.e. 58% multipotent antioxidants, from a total of 152) that also possess >100 pharmacological effects other than antioxidant activity (Table 2, supplementary material). The annotated antioxidant activity in TCMD includes inhibiting radical generation (e.g. inhibiting xanthine oxidase or NADH oxidase), scavenging radicals and preventing lipid peroxidation. As for the other pharmacological effects, antibacterial (28 compounds), antineoplastic (21 compounds), anti-inflammatory (16 compounds) and platelet-aggregation inhibition (16 compounds) are the most common activities. Because radicals are implicated in the etiology of cancer and inflammation, it is understandable that antioxidants can possess antineoplastic and anti-inflammatory properties. However, it is somewhat surprising to observe the antibacterial properties of many antioxidants. This finding is of particular interest to the food industry, because both effects are highly desirable to keep foods as fresh as possible. In addition, four antioxidants – glycyrrhisoflavone, licocoumarone, myristicin, E-piceatannol (Table 2, supplementary material) – exhibit MAO-inhibitory potential, which makes them, as well as related compounds, attractive candidates for testing against AD.

Of the natural multipotent antioxidants identified (Table 2, supplementary material), phenolics are predominant representing 70 compounds (from the total of 88 molecules), and this is in good agreement with a recent study indicating that phenolic compounds are a major contributor to the antioxidant activity in Chinese medicinal plants [34]. This finding also suggests that donating H-atoms (through one-step H-atom transfer or stepwise electron-transfer–proton-transfer) to neutralize radicals is the prevalent mechanism for natural antioxidants. More interestingly, 39 of the 88 multifunctional antioxidants contain either a catechol or pyrogallol moiety. Numerous studies have revealed that catechol and pyrogallol are beneficial for radical scavenging, because the derived catecholic or pyrogallolic radical can be stabilized by an intramolecular hydrogen bond (IHB), as well as by the electron-donating property of *ortho*-OH [35]. In addition, these two groups are also chelators of metal ions. However, the present finding implies that catechol and pyrogallol also play a key role in other pharmacological effects. All this evidence strongly suggests that catechol and pyrogallol could be regarded as multifunctional pharmacophores [6]. Therefore, both groups are good starting points for the design of multipotent antioxidants. Moreover, the presence or absence of catechols and/or pyrogallols will serve as a criterion in screening multipotent antioxidants by virtual high-throughput methodology.

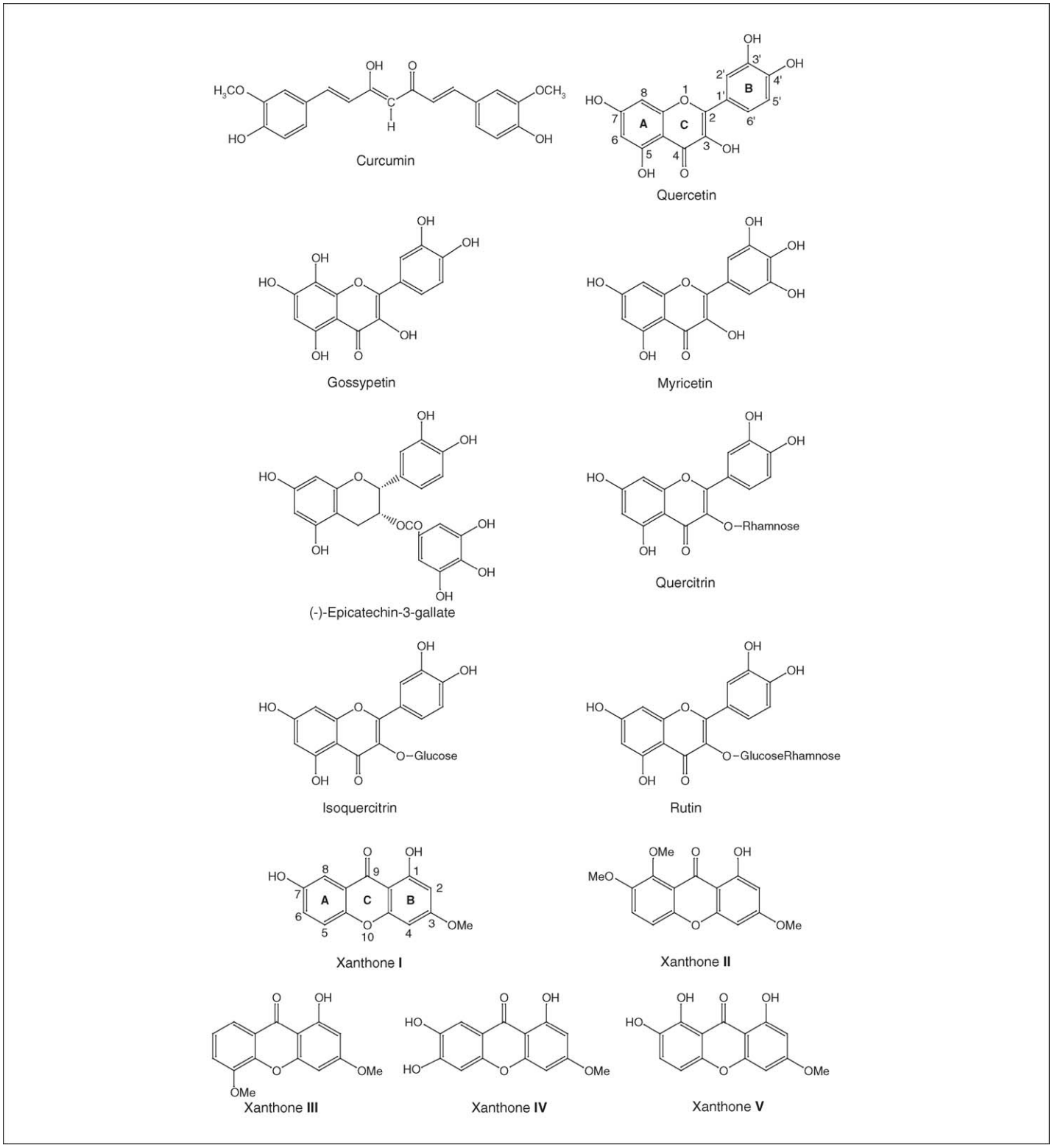

FIGURE 1

Structures of some naturally occurring multipotent antioxidants. All of the antioxidants shown here can scavenge free-radicals and sequester metal ions. In addition, curcumin, quercetin, gossypetin, myricetin and (−)-epicatechin-3-gallate can block Aβ- or tau-aggregation; and quercitrin, isoquercitrin, rutin and quercetin can inhibit monoamine oxidase-B (MAO-B), xanthone I can inhibit MAO-A, xanthone II can inhibit MAO-B and xanthone III can inhibit acetylcholinesterase (AChE).

In conclusion, although the current knowledge on the pharmacological potential of natural products and approved drugs is limited (because novel pharmacological effects are frequently identified for old drugs), the natural products are likely to be a richer source of multipotent antioxidants than the approved drugs. Nevertheless, we think the presently identified natural multifunctional antioxidants represent only the tip of the iceberg. It can be expected that, as knowledge on natural medicines

continues to increase, more and more multifunctional antioxidants will be discovered. Therefore, searching for multipotent antioxidants in compound libraries, especially natural-product collections, could prove to be a highly fruitful approach.

Design of multipotent antioxidants

To improve the process of discovering multipotent antioxidants a rational-design strategy can be employed. The most up-to-date rational-design approach is to connect an antioxidant group and other pharmacophores using a linker. Some successful examples have been identified and are outlined in this review.

In an attempt to improve the efficacy of marketed AD-modifying drugs such as tacrine (an AChE inhibitor), Rosini *et al.* [36] incorporated lipoic acid into the tacrine structure producing lipocrine (**1**, Figure 2). However, Rodríguez-Franco *et al.* [37] coupled tacrine to melatonin, a pineal neurohormone and a preventive antioxidant (**2**, Figure 2). It is interesting to note that these designed hybrid molecules possessed markedly enhanced activity with respect to both AChE activity and antioxidant properties – compared with both of the prototypic molecules used to produce the hybrid structures [36,37].

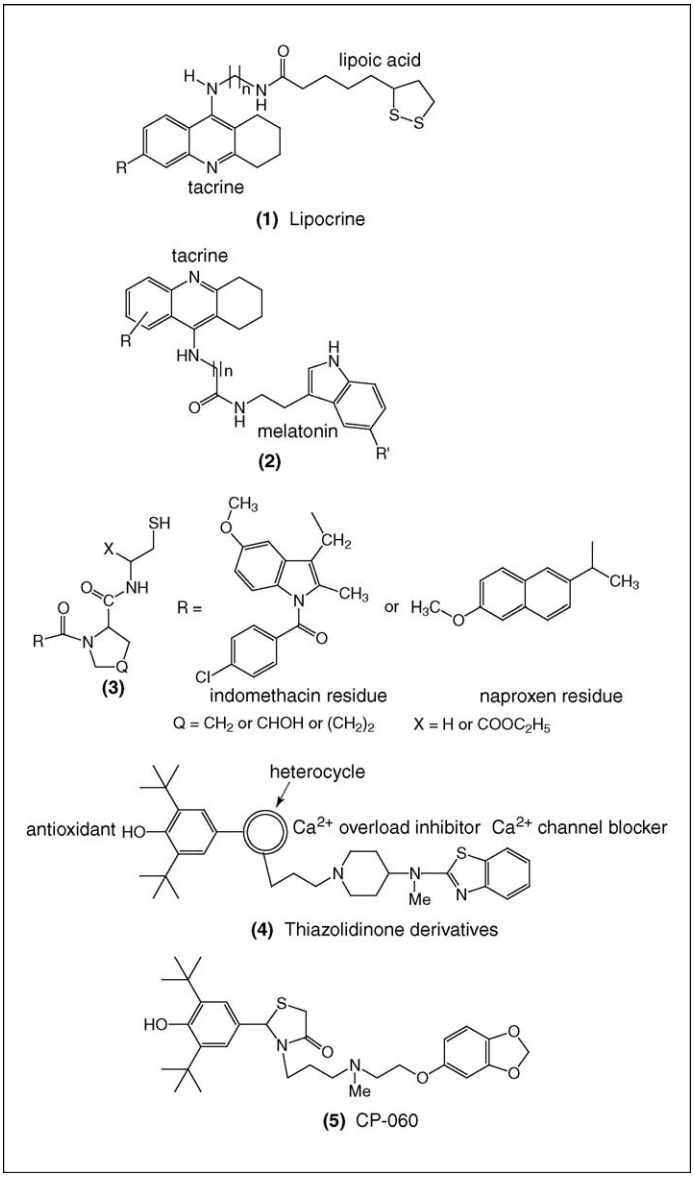

FIGURE 2

Structures of some rationally designed multipotent antioxidants. Besides antioxidant activity, **(1)** and **(2)** can inhibit acetylcholinesterase (AChE), **(3)** holds anti-inflammatory ability, and **(4)** and **(5)** can reduce Ca^{2+} overload.

Because inflammation and oxidative stress have been implicated in the pathogenetic processes underpinning some neurodegenerative diseases, Doulgkeris *et al.* [38] attempted to combine nonsteroidal anti-inflammatory drugs (NSAIDs), such as indomethacin or naproxen, and antioxidants, such as cysteamine or cysteine ethyl ester, into a proline-based framework (proline is part of the pharmacophore for nootropic and antiamnesic activity) (**3**, Figure 2). The resultant hybrid molecules not only retain anti-inflammatory and antioxidant activity but also have been found to possess hypocholesterolemic properties and a significantly reduced potential for gastrointestinal toxicity [38].

Besides their use in neurodegenerative diseases, multipotent antioxidants have attracted significant attention with respect to their potential for the treatment of other complex diseases. Because damage of cardiomyocytes and the functional failure of heart tissue is highly related to oxidative stress and Ca^{2+} overload, multipotent antioxidants might be able to ameliorate ischemic heart disease via this route. Kato *et al.* [39] designed and synthesized novel Ca^{2+} antagonists (thiazolidinone derivatives, **4**, Figure 2) that could reduce Ca^{2+} overload, and exhibit antioxidant activity by the hybridization of antioxidant, Ca^{2+} overload inhibitor and Ca^{2+} channel blocker pharmacophores. Of those compounds produced by this approach, CP-060 (**5**, Figure 2) appeared to be the most promising, in that it possesses a well-balanced combination of the three afore mentioned activities *in vitro* [40], and it has been shown to have strong cardioprotective effects in animal models [41,42].

In an attempt to produce molecules with combined vasorelaxant and antioxidant properties, Antonello *et al.* [43] designed and synthesized a series of hybrid compounds by replacing the furoyl moiety of prazosin, an α_1-adrenoreceptor antagonist, with the lipoyl fragment of lipoic acid [or with 1,4-naphthoquinone (both are universal antioxidants)]. One of the resultant molecules displayed an antiproliferative activity in a carcinoma cell model, greater than that of the prototypic α_1-adrenoreceptor antagonist.

Despite the preliminary success of the present rational design approaches, the structural characteristics of rationally designed multipotent conjugates seem so different from those of their naturally occurring counterparts. For instance, the group of designed agents is composed of two or more isolated parts, linked by spacers of different lengths, and each part is directed towards a particular target (i.e. the radical or enzyme). Whereas, the group of naturally occurring agents shows a seamless framework, indicating that the pharmacophores for various different targets are well merged. The unnatural body plan of designed multifunctional antioxidants might be responsible for their potential toxicity and might yet prove to be a hurdle in the path of their further development. Clearly, an in-depth understanding of natural design will be very helpful to the rational design of multipotent antioxidants.

To elucidate some elements of natural strategy, one can use the flavonoid quercetin (Figure 1) as an example for some in-detail analyses, because quercetin is a typical multifunctional antioxidant with strong radical-scavenging properties and an ability to

inhibit in excess of ten separate enzymes. SAR analyses of quercetin analogues as enzyme inhibitors have revealed that the five hydroxyls and the 4-oxo group play a key role in binding to targets [44–46]. Hydroxyl groups can serve as H-donors and -acceptors, whereas the 4-oxo group only acts as a H-acceptor. By contrast, the hydroxyl groups are also the active sites for scavenging radicals by donating H-atoms. In particular, the catechol moiety makes important contributions, not only to quercetin's antioxidant potential (through neutralizing radicals and chelating metal ions) but also to its enzyme-inhibitory effects (through forming H-bonds with targets) [44,46], which provides further evidence to support the conclusion that catechol is a good starting point for designing multipotent antioxidants. Thus, one might imagine that the incorporation of a catechol moiety (which in some cases might require the addition of only one hydroxyl group) into an enzyme inhibitor could be a shortcut to the design of seamless multipotent antioxidants. This strategy sounds very promising but it does not necessarily work in every case. For instance, some xanthones have been shown to have high MAO-A inhibiting potential [e.g. xanthone I in Figure 1 (IC_{50} = 8 μM)] [30]. To improve the antioxidant activity of the xanthone, one can substitute a hydroxyl group at the 6- or 8-position, producing a catechol-containing xanthone. This design definitely favors radical scavenging of xanthones, as revealed by experimental and theoretical investigation [28,29,47]. However, this design impairs MAO-A inhibition. The IC_{50}s of both catechol-containing xanthones (IV and V, Figure 1) increase to 25 μM and 24 μM, respectively – from an initial value of 8 μM [30]. This example indicates the difficulty of reaching a balance between enzyme inhibition and radical scavenging in a merged molecular framework. A comparison between the structures of flavonoids (e.g. quercetin) and xanthones suggests that the deficiencies in xanthone design perhaps arise from their rigid structure. The perfect conjugation between rings A, B and C in xanthones I–V makes such structures less-active multipotent antioxidants than flavonoids. This could be because, in flavonoids, the B-ring can rotate around the C2–C1′ bond allowing conformational adaptation to different targets. Therefore, before beginning rational design through an integrating strategy, one should make a thorough quantitative SAR (QSAR) analysis for the enzyme inhibitors. Although catechol and pyrogallol are good starting points for the design of multipotent antioxidants, the way ahead is still fraught with potential stumbling blocks.

Conclusion

Finding antioxidants containing other pharmacological properties represents a new trend in antioxidant (and even drug) development. The new concept can be fulfilled by screening natural-product libraries and drug collections, and by coupling the active center of antioxidants with pharmacophores of enzyme inhibitors. Naturally occurring multipotent antioxidants are not only valuable drug candidates but also serve as illustrations of natural strategies in the design of multifunctional antioxidants that will, in turn, benefit our rational-design practice. Through a preliminary analysis, we reveal that catechol and/or pyrogallol moieties, and conformational flexibility, will probably constitute the core of the natural strategy.

Acknowledgements

We would like to thank Dr De-Xin Kong for assisting in searching the TCMD and CMC databases.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.drudis.2006.06.007.

References

1 Keith, C.T. *et al.* (2005) Multicomponent therapeutics for networked systems. *Nat. Rev. Drug Discov.* 4, 71–78
2 Mencher, S.K. and Wang, L.G. (2005) Promiscuous drugs compared to selective drugs (promiscuity can be a virtue). *BMC Clin. Pharmacol.* 5, 3
3 Morphy, R. *et al.* (2004) From magic bullets to designed multiple ligands. *Drug Discov. Today* 9, 641–651
4 Morphy, R. and Rankovic, Z. (2005) Designed multiple ligands. An emerging drug discovery paradigm. *J. Med. Chem.* 48, 6523–6543
5 Youdim, M.B.H. and Buccafusco, J.J. (2005) Multi-functional drugs for various CNS targets in the treatment of neurodegenerative disorders. *Trends Pharmacol. Sci.* 26, 27–35
6 Zhang, H.-Y. (2005) One-compound-multiple-targets strategy to combat Alzheimer's disease. *FEBS Lett.* 579, 5260–5264
7 Espinoza-Fonseca, L.M. (2006) The benefits of the multi-target approach in drug design and discovery. *Bioorg. Med. Chem.* 14, 896–897
8 Finkel, T. (2005) Radical medicine: treating ageing to cure disease. *Nat. Rev. Mol. Cell Biol.* 6, 971–976
9 Barnham, K.J. *et al.* (2004) Neurodegenerative diseases and oxidative stress. *Nat. Rev. Drug Discov.* 3, 205–214
10 Brown, D.R. and Kozlowski, H. (2004) Biological inorganic and bioinorganic chemistry of neurodegeneration based on prion and Alzheimer diseases. *Dalton Trans.* 13, 1907–1917
11 Godfraind, T. (2005) Antioxidant effects and the therapeutic mode of action of calcium channel blockers in hypertension and atherosclerosis. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 360, 2259–2272
12 Litwinienko, G. and Ingold, K.U. (2004) Abnormal solvent effects on hydrogen atom abstraction. 2. Resolution of the curcumin antioxidant controversy. The role of sequential proton loss electron transfer. *J. Org. Chem.* 69, 5888–5896
13 Aggarwal, B.B. *et al.* (2003) Anticancer potential of curcumin: preclinical and clinical studies. *Anticancer Res.* 23, 363–398
14 Chainani-Wu, N. (2003) Safety and anti-inflammatory activity of curcumin: a component of tumeric (*Curcuma longa*). *J. Altern. Complement. Med.* 9, 161–168
15 Chattopadhyay, I. *et al.* (2004) Turmeric and curcumin: biological actions and medicinal applications. *Curr. Sci.* 87, 44–53
16 Ono, K. *et al.* (2004) Curcumin has potent anti-amyloidogenic effects for Alzheimer's β-amyloid fibrils *in vitro*. *J. Neurosci. Res.* 75, 742–750
17 Yang, F. *et al.* (2005) Curcumin inhibits formation of amyloid β oligomers and fibrils, binds plaques, and reduces amyloid *in vivo*. *J. Biol. Chem.* 280, 5892–5901
18 Baum, L. and Ng, A. (2004) Curcumin interaction with copper and iron suggests one possible mechanism of action in Alzheimer's disease animal models. *J. Alzheimers Dis.* 6, 367–377
19 Barik, A. *et al.* (2005) Evaluation of a new copper(II)-curcumin complex as superoxide dismutase mimic and its free radical reactions. *Free Radic. Biol. Med.* 39, 811–822
20 Shen, L. *et al.* (2005) A theoretical study on Cu(II)-chelating properties of curcumin and its implications for curcumin as a multipotent agent to combat Alzheimer's disease. *J. Mol. Struct. THEOCHEM* 757, 199–202
21 Chandra, V. *et al.* (1998) Prevalence of Alzheimer's disease and other dementias in rural India: the Indo-US study. *Neurology* 51, 1000–1008
22 Evans, D.A. *et al.* (1989) Prevalence of Alzheimer's disease in a community population of older persons. Higher than previously reported. *JAMA* 262, 2551–2556
23 Rice-Evans, C.A. *et al.* (1996) Structure-antioxidant activity relationships of flavonoids and phenolic acids. *Free Radic. Biol. Med.* 20, 933–956
24 Taniguchi, S. *et al.* (2005) Inhibition of heparin-induced tau filament formation by phenothiazines, polyphenols, and porphyrins. *J. Biol. Chem.* 280, 7614–7623

25 Ono, K. *et al.* (2003) Potent anti-amyloidogenic and fibril-destabilizing effects of polyphenols *in vitro*: implications for the prevention and therapeutics of Alzheimer's disease. *J. Neurochem.* 87, 172–181

26 Kim, H. *et al.* (2005) Effects of naturally occurring compounds on fibril formation and oxidative stress of β-amyloid. *J. Agric. Food Chem.* 53, 8537–8541

27 Lee, M.-H. *et al.* (2001) Monoamine oxidase B and free radical scavenging activities of natural flavonoids in *Melastoma candidum* D. Don. *J. Agric. Food Chem.* 49, 5551–5555

28 Hay, A.E. *et al.* (2004) Antioxidant xanthones from *Garcinia vieillardii*. *J. Nat. Prod.* 67, 707–709

29 Lee, B.W. *et al.* (2005) Antioxidant and cytotoxic activities of xanthones from *Cudrania tricuspidata*. *Bioorg. Med. Chem. Lett.* 15, 5548–5552

30 Gnerre, C. *et al.* (2001) Natural and synthetic xanthones as monoamine oxidase inhibitors: biological assay and 3D-QSAR. *Helv. Chim. Acta* 84, 552–570

31 Brühlmann, C. *et al.* (2004) Screening of non-alkaloidal natural compounds as acetylcholinesterase inhibitors. *Chem. Biodivers.* 1, 819–829

32 Traditional Chinese medicine database, Chinese edition (2005) Accelrys Inc., Beijing

33 Comprehensive medicinal chemistry, Release 2004.1, MDL Information Systems Inc., San Leandro, CA, USA

34 Wong, C.-C. *et al.* (2006) A systematic survey of antioxidant activity of 30 Chinese medicinal plants using the ferric reducing antioxidant power assay. *Food Chem.* 97, 705–711

35 Zhang, H.-Y. (2005) Structure-activity relationships and rational design strategies for radical-scavenging antioxidants. *Curr. Computer-Aided Drug Des.* 1, 257–273

36 Rosini, M. *et al.* (2005) Rational approach to discover multipotent anti- Alzheimer drugs. *J. Med. Chem.* 48, 360–363

37 Rodríguez-Franco, M.I. *et al.* (2006) Novel tacrine-melatonin hybrids as dual-acting drugs for Alzheimer disease, with improved acetylcholinesterase inhibitory and antioxidant properties. *J. Med. Chem.* 49, 459–462

38 Doulgkeris, C.M. *et al.* (2006) Synthesis and pharmacochemical study of novel polyfunctional molecules combining anti-inflammatory, antioxidant, and hypocholesterolemic properties. *Bioorg. Med. Chem. Lett.* 16, 825–829

39 Kato, T. *et al.* (1998) Novel calcium antagonists with both calcium overload inhibition and antioxidant activity. 1. 2-(3,5-di-tert-butyl-4-hydroxyphenyl)-3-(aminopropyl)thiazolidi-nones. *J. Med. Chem.* 41, 4309–4316

40 Kato, T. *et al.* (1999) Novel calcium antagonists with both calcium overload inhibition and antioxidant activity. 2. structure-activity relationships of thiazolidinone derivatives. *J. Med. Chem.* 42, 3134–3146

41 Koga, T. *et al.* (1998) The protective effects of CP-060S on ischaemia-and reperfusion-induced arrhythmias in anaesthetized rats. *Br. J. Pharmacol.* 123, 1409–1417

42 Suzuki, Y. *et al.* (1998) CP-060S, a novel cardioprotective drug, limits myocardial infarct size in anesthetized dogs. *J. Cardiovasc. Pharmacol.* 31, 400–407

43 Antonello, A. *et al.* (2005) Design, synthesis, and biological evaluation of prazosin-related derivatives as multipotent compounds. *J. Med. Chem.* 48, 28–31

44 Agullo, G. *et al.* (1997) Relationship between flavonoid structure and inhibition of phosphatidylinositol 3-kinase: A comparison with tyrosine kinase and protein kinase C inhibition. *Biochem. Pharmacol.* 53, 1649–1657

45 Maliar, T. *et al.* (2004) Structural aspects of flavonoids as trypsin inhibitors. *Eur. J. Med. Chem.* 39, 241–248

46 Ji, H.-F. and Zhang, H.-Y. Theoretical evaluation of flavonoids as multipotent agents to combat Alzheimer's disease. *J. Mol. Struct. (Theochem)* in press

47 Ji, H.-F. *et al.* (2005) Theoretical elucidation on structure-activity relationships of antioxidant xanthones. *QSAR Combin. Sci.* 24, 826–830