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viewpoint

Natural products and drug discovery

Can thousands of years of ancient medical knowledge lead us to new and powerful drug combinations in the fight against cancer and dementia?

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The medicinal use of natural products—compounds that are derived from natural sources such as plants, animals or micro-organisms—precedes recorded human history probably by thousands of years. Palaeoanthropological studies at the cave site of Shanidar, located in the Zagros Mountains of Kurdistan in Iraq, have suggested that more than 60,000 years ago, Neanderthals might have been aware of the medicinal properties of various plants, as evidenced by pollen deposits in one of the graves at the site (Solecki, 1975). Over the ensuing millennia, humankind discovered and made use of an enormous range of natural compounds; the latest version of the *Dictionary of Natural Products* (DNP; http://dnp.chemnetbase.com) has just over 214,000 entries.

Throughout our evolution, the importance of natural products for medicine and health has been enormous. Since our earliest ancestors chewed on certain herbs to relieve pain, or wrapped leaves around wounds to improve healing, natural products have often been the sole means to treat diseases and injuries. In fact, it has only been during the past decades that natural products have taken a secondary role in drug discovery and drug development, after the advent of molecular biology and combinatorial chemistry made possible the rational design of chemical compounds to target specific molecules. The past few years, however, have seen a renewed interest in the use of natural compounds and, more importantly, their role as a basis for drug development. The modern tools of chemistry and biology—in particular, the various '-omics' technologies—now allow scientists to detail the exact nature of the biological effects of natural compounds on the human body, as well as to uncover possible synergies, which holds much promise for the development of new therapies against many devastating diseases, including dementia and cancer.

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Owing to the diverse biological activities and medicinal potentials of natural products, nearly every civilization has accumulated experience and knowledge of their use. The oldest medical text comes from ancient Mesopotamia, *circa* 2600 BC, and is written on hundreds of clay tablets in cuneiform. It describes approximately 1,000 plants and plant-derived substances, such as the oils of *Cedrus* species (cedar), the resin of *Commiphora myrrha* (myrrh) and the juice of the poppy seed *Papaver somniferum* (Newman *et al*, 2000). Many of these herbs and formulations are still used today. The ancient Egyptian *Ebers Papyrus*, dating from around 1550 BC, contains about 800 complex prescriptions and more than 700 natural agents such as *Aloe vera* (aloe), *Boswellia carteri* (frankincense) and the oil of *Ricinus communis* (castor) (Zhong & Wan, 1999). The famous Greek physician, Hippocrates of Cos (*circa* 460–377 BC), collected more than 400 natural agents and described their use in his *Corpus Hippocraticum*. He mentioned using melon juice as a laxative, described the diuretic effect of the juice from *Ornithogalum caudatum* (squill) and detailed how to use an extract from *Atropa belladonna* as an anaesthetic. He also advised using an extract of *Veratrum album* (white hellebore) as an emetic and how to use olive oil to improve wound healing (Castiglioni, 1985). Roman physicians built on this extensive know ledge and added their own insights and experience. Pedanius Dioscorides (*circa* 40–90 AD) compiled *De Materia Medica*, which described the dosage and efficacy of about 600 plant-derived medicines and laid the foundations of pharmacology in Europe (Wermuth, 2003). Galen (129–200 AD), another famous Greek physician and pharmacist, recorded 540 plant-derived medicines and demonstrated that herbal extracts contain not only beneficial components, but also harmful ingredients (Cai, 1992; Cheng & Zhen, 2004).

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Natural product-based medicines also flourished in the Orient. *Charaka Samhita,* the first treatise devoted to the concepts and practice of Indian Ayurveda, was written around 900 BC and contains 341 plant-derived medicines. The *Sushruta Samhita* (*circa* 600 BC) was mainly devoted to surgical practices, but also described 395 medicinal plants and 57 animal-derived products (Dev, 1999).

Traditional Chinese medicine (TCM) is also famous for its extensive use of natural products. The most primitive Chinese medicinal book, *Wu Shi Er Bing Fang*—which translates to *Prescriptions for Fifty-Two Diseases*—was compiled around

350 BC and lists 247 natural agents and about 150 combinatorial drug formulae, along with practical advice regarding the properties, efficacies and synergies of natural medicines (Wan & Zhong, 1990; Jiao & Wang, 2005). The monograph *Shen Nong Ben Cao Jing* (*Shen Nong Materia Medica*) was compiled during the Eastern Han dynasty (25–220 AD) and documented 365 agents, including 252 medicinal plants and 67 medicinal animals (Gao, 2004). The therapeutic effects of many of these agents have been confirmed by subsequent medical practice (Gao, 2004), such as the use of *Coptis chinensis* (coptis root) to treat diarrhoea, *Ephedra sinica* (ephedra herb) as an anti-asthmatic and *Melia azedarach* (chinaberry seed) as an anti-helmintic. In 659 AD, China issued the first national pharmacopaeia, *Xin Xiu Ben Cao* (*Newly Revised Medicinal Materials*, also called *Tang Ben Cao*), which contained 850 agents (Gao, 2004). In 1587 AD, Li Shi-Zhen published his famous work *Ben Cao Gang Mu* (*Compendium of Medicinal Materials*), which recorded 1,892 agents and about 11,000 combinatorial formulae (Gao, 2004).

…we need to move beyond either xenohormesis or co-evolution to explain the biological effects of natural products

Although the ancient Occidental and Oriental medicinal systems developed independently of one other, it is interesting to note that their respective practitioners often used the same natural products to treat similar diseases. For example, both *Shen Nong Ben Cao Jing* and *De Materia Medica* describe the use of an extract from *Tussilago farfara* as an antitussivum to suppress coughing. Hippocrates used an extract of *Veratrum album* (white hellebore) as an emetic, whereas his Chinese counterparts used that of *Veratrum nigrum* (black hellebore). The oil of *Nepeta cataria* (catnip) was used as an antipyretic in Europe for thousands of years, and *Shen Nong Ben Cao Jing* notes the same use for another species of the family, *Nepeta tenuifolia*. As there seems to have been little regular communication between China and Europe 2,000 years ago, this would seem to be an example of the convergent evolution of different medicinal systems (Kong *et al*, 2008a).

Despite the wide use of medicinal plants in the Orient and Occident, their effective components—the specific identity of the chemicals that had the desired therapeutic effects—remained all but unknown until the eighteenth and nineteenth centuries. However, early doctors, such as Galen, did understand that various natural products contained different compounds that would each affect the human body differently.

Modern chemistry has ushered in a new era for the study and use of natural products. Analytical and structural chemistry have provided the tools to purify various compounds and to determine their structures, which, in turn, has given insights into their action on the human body. In 1805, the German pharmacist Friedrich Wilhelm Sertürner (1783–1841) isolated morphine from opium, and it became both the first pure naturally derived medicine and the first to be commercialized, by Merck in 1826. In fact, Western pharmaceutical companies quickly began to prefer purified natural products as ingredients to make drugs, rather than crude extracts. In addition, the elucidation of the molecular structures of many natural products allowed chemists to synthesize them, rather than isolating them from natural sources, which markedly lowered the cost of drug production.

Subsequently, a large number of well-known natural compounds were identified, analysed and synthesized: salicin from *Salix alba* (white willow), emetine from *Cephaelis ipecacuanha* (ipecacuanha), strychnine and brucine from *Strychnos nux-vomica* (strychnos), quinine from *Cinchona ledgeriana* (cinchona bark), colchicine from *Colchicum autumale* (colchicum), caffeine from *Coffea arabica*, nicotine from *Nicotiana tabacum*, atropine from *Atropa belladonna* and cocaine from *Erythroxylum coca*. Many of these compounds are still widely used as drugs. The twentieth century saw the discovery of the antibacterial properties of penicillin, derived from the mould *Penicillium notatum*, which was soon followed by various other antibacterials that gave physicians an enormously powerful weapon in their battle against infectious diseases.

The structural analysis of natural compounds and the ability to synthesize them allowed chemists to modify them in order to suppress or enhance certain characteristics such as solubility, efficiency or stability in the human body. Newman (2008)

…it remains an important challenge to find biologically active compounds and to develop these into new drugs, even if one uses nature for inspiration

estimates that about 60% of the drugs that are now available—including household names such as artemisinin, camptothecin, lovastatin, maytansine, paclitaxel, penicillin, reserpine and silibinin—were either directly or indirectly derived from natural products. Moreover, natural products have also been an invaluable source of inspiration for organic chemists to synthesize novel drug candidates (Beghyn *et al*, 2008; Hunter, 2008; Koehn & Carter, 2005). Some have even claimed that the switch away from natural products to combinatorial chemistry during the 1990s might have led to the current paucity of new drug candidates in the development pipeline (Desai & Chackalamannil, 2008). It is therefore a matter of great scientific, economic and medical interest to analyse and understand why so many natural products are beneficial to human health.

Many chemists and biologists have attempted to explain the puzzle of why so many compounds in nature have biological effects in humans and other species. One explanation that has been widely accepted is that it is the result of long-term co-evolution within biological communities: interacting organisms that evolved in close proximity to one another developed compounds that could influence the biological processes of neighbouring species. As these compounds proved to be advantageous, they became a trait on which natural selection could act, and were retained and improved throughout the course of evolution. Given the similarities between aspects of human physiology and that of other animals, it is not surprising that such molecules can also exert biological effects in humans. For example, many chemicals that plants evolved to defend themselves against herbivores are now used as laxatives, emetics, cardiotonics or muscle relaxants in humans (Briskin, 2000). In addition, humans have taken advantage of some of the discovered properties of natural compounds: those that are able to interact with or suppress the growth of bacteria, for example, are now used as antimicrobial drugs in medicine.

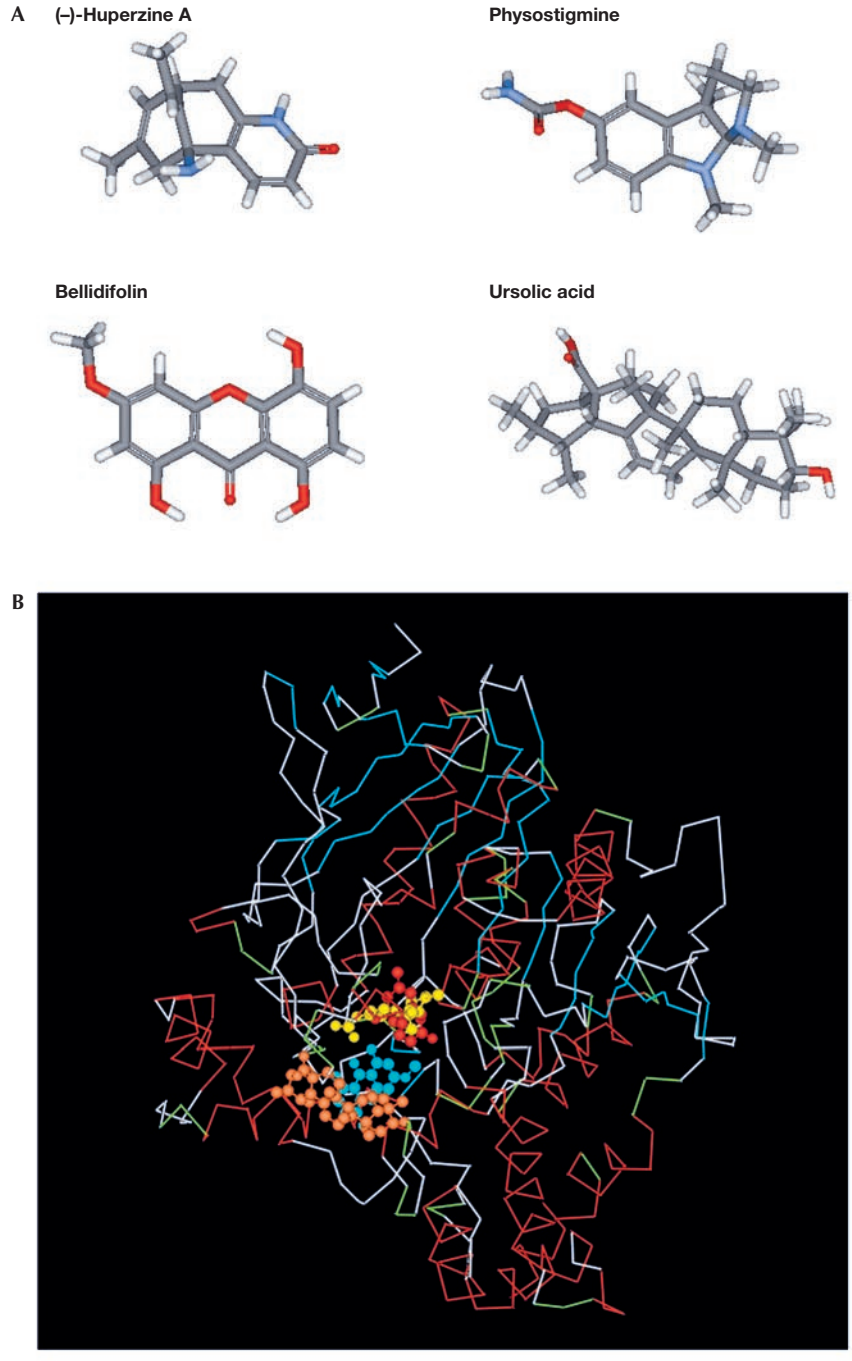

Fig 1 | Molecular structures of natural inhibitors of acetylcholinesterase. (**A**) (–)-Huperzine A (EC_{50} = 0.1 nM), physostigmine (EC_{50} = 0.6 nM), bellidifolin (EC_{50} = 0.15 nM) and ursolic acid (EC_{50} = 7.5 nM). (**B**) Binding sites of these inhibitors on the acetylcholinesterase. (–)-Huperzine A is shown in red, physostigmine in yellow, bellidifolin in cyan and ursolic acid in orange. The X-ray structure of acetylcholinesterase and (–)-huperzine A was obtained from the Protein Data Bank (entry 1VOT). The binding of the other three inhibitors was calculated by using the FlexX module of SYBYL 7.0.

The co-evolution theory also explains other phenomena, including synergistic effects. Several years ago, Lewis and co-workers showed that the high antimicrobial potential of *Berberis* spp. (Pepperidge bush) is caused not only by antimicrobial agents such as berberine, but also by multidrug-resistance (MDR) inhibitors such as 5′-methoxyhydnocarpin (Stermitz *et al*, 2000). The latter have no microbicidal activity of their own, but seemingly potentiate the antibiotic effects of other molecules. This phenomenon could be explained in terms of co-evolution and the classic 'arms race' between host and pathogen. Plants that evolved antimicrobials were able to defend themselves against pathogenic bacteria; pathogens that evolved resistance mechanisms, such as MDR pumps, were able to break plant defences; in turn, plants that developed MDR inhibitors had a significant evolutionary advantage (Li & Zhang, 2008).

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Some compounds exert their biological effects by mimicking endogenous metabolites, including ligands, hormones or other molecules involved in inter- and intracellular signal transduction. For example, some alkaloids—such as anagyrine from *Anagyris foetida*, cytosine from *Laburnum anagyroides*, lupanine from *Cytisus scoparius* [Syn. *Spartium scoparium*] or sparteine from *Chelidonium majus*—affect neuroreceptors by forming a quaternary nitrogen configuration that resembles a structural motif present in most neurotransmitters (Wink, 2003). In other cases, different organisms use similar molecules for the same purpose: brassinolids are plant steroid hormones, which regulate cell division and cell development in the plant, and that are structurally similar to human growth-regulating steroids.

Recently, Howitz & Sinclair (2008) proposed an alternative hypothesis, called xenohormesis, to explain the origin of beneficial natural products. According to their theory, the common ancestor of plants and animals was able to synthesize a large number of stress-induced secondary metabolites. Animals and fungi that feed on plants gradually lost the capacity to synthesize these low-weight molecular compounds, but retained the ability to sense these chemical cues in plants, possibly in order to detect when plants were stressed and gain an early warning of changing environmental conditions.

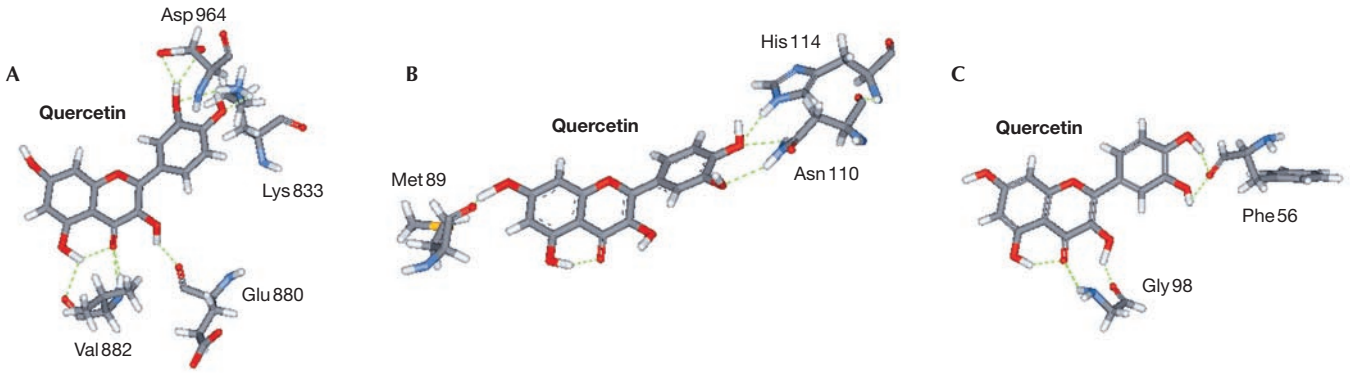

Fig 2 | Binding modes of quercetin. Binding to (**A**) phosphatidylinositol-3-kinase; (**B**) helix–turn–helix-type transcriptional regulator; and (**C**) 3-hydroxyisobutyryl-CoA hydrolase.

This theory is at least partly supported by the finding that certain human genes have homologues in plants and microbes—at least to the extent that plants and animals use similar signalling molecules and receptors in some cases. Indeed, a comparative genomic analysis revealed that 70% of cancer-related human genes have orthologues in *Arabidopsis thaliana* (Jones *et al*, 2008). Thus, given the similarity of many plant and human genes, it seems obvious that some secondary metabolites produced by plants to modulate their own metabolism should also be able to bind to molecules that have a role in human disease. For example, multidrug resistance-like proteins that are used by *Arabidopsis* to transport auxin have orthologues in humans that are crucial for the transport of anti-cancer agents; auxin-distribution modulators such as flavonoids from *Arabidopsis* can inhibit P-glycoprotein (MDR1) in various human cancer cells (Taylor & Grotewold, 2005).

However, neither theory explains the full power of natural products. First, some natural compounds—for example, curcumin, resveratrol or quercetin—can bind to many target molecules implicated in human disease (Aggarwal & Shishodia, 2006; Goel *et al*, 2008; Ji & Zhang, 2008). Some of these targets such as acetylcholinesterase (AChE) or monoamine oxidases A and B, are unique to animals and have no homologues in plants that produce these natural agents.

Second, the health effects of many plant compounds are not intrinsic to those molecules but are a consequence of the human digestive system processing their metabolites. Willow bark has long been used to ease pain and reduce fever; yet, although the effective component is salicylic acid, willow bark only contains the precursor salicin, which is hydrolysed in the small intestine to salicylic alcohol and further oxidized to salicylic acid by intestinal bacteria (Akao *et al*, 2002). Another example is phenolic glucoside arbutin, which is used to treat urinary tract infections. This compound itself is ineffective until it is hydrolysed and oxidized to hydroquinone in the human body. Further examples are the sennosides, which are converted into laxative anthrones by bacteria in the gut. Similarly, conjugated phytoestrogens have to be hydrolysed in the stomach or the gut to exert their oestrogen-like effects (Hostettmann & Marston, 2007). Strictly speaking, these plant molecules are not drugs, but proto-drugs.

> **…natural products provide important clues for identifying and developing synergistic drugs that, so far, research has largely neglected**

Third, some of the biological effects of these natural products—such as slowing down the progress of Alzheimer disease or dementia—give no obvious advantage to the producer of the agent, and so their action cannot be explained as the result of co-evolution. Taken together, these puzzling observations seem to suggest that we need to move beyond either xenohormesis or co-evolution to explain the biological effects of natural products. In turn, this has stimulated our interest in the three-dimensional structures of natural product–target complexes.

Modern structural biology has made possible the exact determination of the crystal structures of protein target–inhibitor complexes, such as HIV-1 protease–lopinavir complex or AChE–huperzine A complex. These studies have revealed that, in most cases, the relationship between a target and a native inhibitor is not a rigid lock and key combination. First, the same macromolecule can bind to distinct inhibitors. By way of example, natural inhibitors of AChE can have different structures (Fig 1A), but have comparable inhibitory activities (Mukhejee *et al*, 2007). The explanation for this is that the binding cavity of the protein is larger than the small inhibitor, which means that there are many binding modes for these agents to modify enzyme activity. Fig 1B shows how four AChE inhibitors are able to occupy different parts of the protein.

Second, many natural compounds can bind to diverse proteins. Quercetin, for example, can inhibit enzymes with distinct architectures such as phosphatidylinositol-3-kinase, which has a protein kinase-like fold; helix–turn–helix-type transcriptional regulator, which has a tetracycline repressor-like fold; and 3-hydroxyisobutyryl-CoA hydrolase, which has a ClpP/crotonase fold (Fig 2A–C). This phenomenon is likely to result from the fact that ligand-binding cavities are less diverse than protein architectures (Ji *et al*, 2007; McArdle & Quinn 2007); that both natural products and proteins are flexible entities, which allows them to adapt their configuration; and that natural

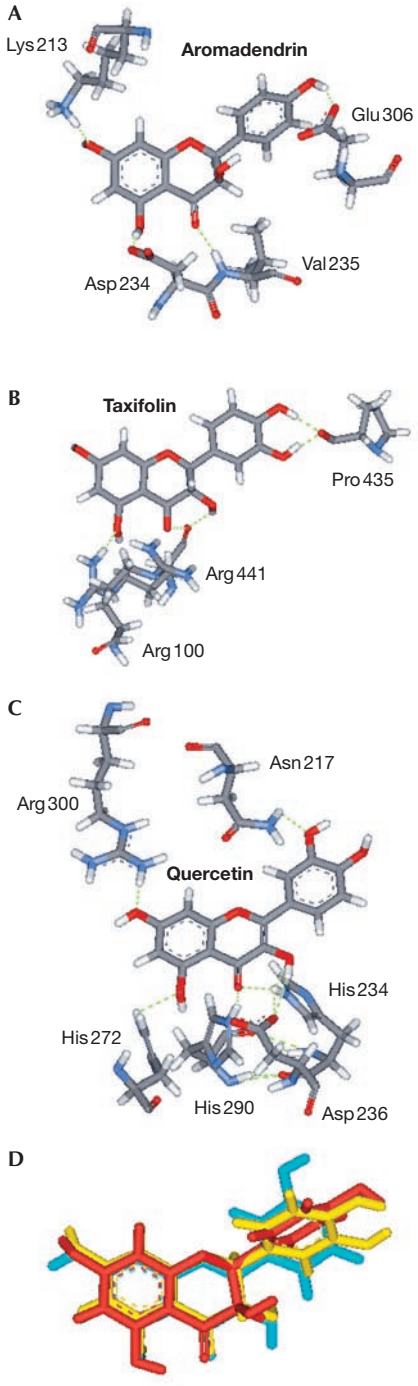

Fig 3 | Binding modes of quercetin and its precursors. (**A**) Aromadendrin with flavanone 3-dioxygenase; (**B**) taxifolin with flavonoid 3',5'-hydroxylase; (**C**) quercetin with flavonol synthase. (**D**) Quercetin (cyan) superimposed with aromadendrin (red) and taxifolin (yellow). The structures of flavonoid 3',5'-hydroxylase and flavonol synthase were modelled based on the crystal structures of cytochrome P450 from *Homo sapiens* (similarity: 49%) and anthocyanidin synthase from *Arabidopsis thaliana* (similarity: 62%) respectively, by using the homology module of Insight II.

products usually have diversified binding groups, a subset of which is sufficient to bind to the target, as explained below.

In fact, the reason why natural products are able to bind to multiple target molecules might be due to their mode of generation. Many of the natural compounds used in medicine have a complex structure and their synthesis involves a range of enzymes. In the case of quercetin biosynthesis, for example, no less than three synthetases are involved in the final steps, each of which has distinct architectures and molecule-binding cavities, and all of which the quercetin molecule under synthesis must be able to interact with (Fig 3A–C). The core structure of quercetin has therefore inherited diverse binding groups and a certain level of flexibility in order to be able to bind to these enzymes (Fig 3). This diversity and flexibility thus allows it to interact with other unintended proteins with similar binding sites.

In the early 1990s, many pharmaceutical companies concentrated their research efforts on combinatorial chemistry and high-throughput screening to generate and identify new drug candidates. However, this strategic shift did not bring the expected returns in terms of new drug candidates. In 2007, only 17 new drug entities were approved, compared with 53 in 1996. Moreover, given the average duration of drug discovery and development, most of the latter were originally identified in the 1980s (Hughes, 2008). Pharmacists and chemists are therefore turning their attention back to nature's toolbox: indeed, some promising drug candidates such as huperzine A, triptolide, celastrol, capsaicin and curcumin, have come from this recent focus on natural agents (Ji & Zhang, 2008; Corson & Crews, 2007). However, it remains an important challenge to find biologically active compounds and to develop these into new drugs, even if one uses nature for inspiration. Their complex evolutionary histories mean that the structures of natural compounds are highly likely to generate secondary effects and their efficacy often depends on synergistic interactions with other components (Keith *et al*, 2005).

Nonetheless, the popularity of natural products will continue simply because they are a matchless source of novel drug leads and inspiration for the synthesis of non-natural molecules (Baker *et al*, 2007; Beghyn *et al*, 2008; Harvey, 2008; Hunter, 2008; Koehn & Carter, 2005). In addition, natural products provide important clues for identifying and developing synergistic drugs that, so far, research has largely neglected. Most modern drug discovery has been based on a 'one-disease–one-target–one-drug' strategy. The pathogenesis of many diseases involves multiple factors, however, and a selective compound against a single target often fails to achieve the desired effect, particularly in cancer therapy. Consequently, there is increasing interest in 'multi-component therapeutics' to overcome the challenge of 'more investment, fewer drugs' (Keith *et al*, 2005; Schmidt *et al*, 2007; Kong *et al*, 2008b). This new strategy could have several advantages as it would modulate biological networks rather modestly and might therefore be more efficient in dealing with complex diseases (Csermely *et al*, 2005; Dancey & Chen 2006; Zimmermann *et al*, 2007). Moreover, it could prevent, or at least slow down, the development of resistance against many antibiotics, antimalarials and anti-cancer drugs.

The prospect of new and better drug combinations is enticing, and natural compounds hold great promise. Nevertheless, a huge challenge remains to identify natural compounds—or naturally inspired compounds—that can be combined to be effective against human disease. The enormous number of possible drug combinations, the inherent risks of harmful drug–drug interactions, the possible antagonistic effects and the unpredictable pharmacokinetic properties of multi-component formulations must still be addressed. As pointed out above, we have a rich historical record from ancient physicians about how to use natural medicines alone and in combination, which might provide important clues for developing new drugs (Schmidt *et al*, 2007; Verpoorte *et al*, 2009).

To make the best use of our forbearers' knowledge, we need to analyse these medical formulae and elucidate their synergistic effects. We already know of some compounds that are more powerful in combination than alone: for example, the combination of Realgar, *Indigo naturalis*, *Radix salviae miltiorrhizae* and *Radix pseudostellariae*

constitutes a formula in TCM that has proven effective against human acute promyelocytic leukaemia (Huang *et al*, 1995). Its synergistic effect was recently attributed to the direct anti-cancer properties of tetra-arsenic tetrasulphide from Realgar and the complementary effects of indirubin and tanshinone IIA from *Indigo naturalis* and *Radix salviae miltiorrhizae*, respectively, which enhance the transport of tetra-arsenic tetrasulphide into target cells and thus potentiates its efficacy (Wang *et al*, 2008).

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Similarly, the combination of *Coptidis rhizoma* and *Evodia rutaecarpa,* known as *Zuo Jin Wan,* has been used for more than 700 years in TCM to treat gastric conditions. This herbal combination contains possible drug candidates such as berberine and calystigine—antibiotics and potential inhibitors of *Helicobacter pylori*—limonene, an antineoplastic agent, and obacunone and rutecarpine, which are inhibitors of cancer-cell multidrug resistance, which are all relevant to treating gastric conditions including cancers (Kong *et al*, 2008c). Thus, this naturally occurring, effective combination of chemicals points us towards new combinations and uses for those drugs that we already have.

TCM has also accumulated experience of treating dementia using plant-derived medicines. A recent analysis of 1,232 TCM formulae revealed that the most common combination of herbs used for this purpose was *Rhizoma chuanxiong, Radix salviae miltiorrhizae, Radix polygalae tenuifoliae* and *Rhizoma acori tatarinowii*. These herbs contain hundreds of natural products, some of which have anti-dementia effects. For example, tetramethylpyrazine and 3-*n*-butylphthalide from *Rhizoma chuanxiong* are neuronal injury inhibitors; 9-*cis*,12-*cis*-linoleic acid from *Rhizoma chuanxiong* is effective against cognition disorders; miltirone from *Radix salviae miltiorrhizae* is an anxiolytic; and baicalin from *Radix salviae miltiorrhizae* has anti-inflammatory and antioxidant potential. In addition, *Radix polygalae tenuifoliae* contains 1-hydroxy-3,6,7-trimethoxy xanthone, which is an antidiabetic agent and could be used to treat diabetes-related cognitive disorders (Kong *et al*, 2008b).

These formulae also contain important clues about synergistic effects that could provide new leads for the fight against complex diseases such as cancer and dementia. Most of these compounds are available as pure chemicals and some have already been used in the clinic for many years. This accumulated experience from TCM and other ancient medicinal practices could allow modern researchers to design and control synergistic effects far better than was possible by blending crude natural products.

As mentioned above, a strategy to analyse and modify synergistic drug combinations still poses considerable challenges for research, clinical development and regulatory agencies. Nonetheless, modern pharmaceutical research, using the powerful tools of genomics, proteomics, metabolomics and synthetic and combinatorial chemistry, could learn a lot from the historical record of using natural products to fight diseases—after all, this knowledge represents the cumulative experience of thousands of years of medical practice.

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