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This article fosters a multi-target concept that makes use of the apparent beneficial broad target profile of well-characterized anti-inflammatory natural lead compounds with privileged structures.

Multi-target approach for natural products in inflammation

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Although an increasing number of studies show the (pre)clinical efficiency and safety of multi-target natural products, they are still underrepresented as starting points for multi-target drug discovery. This article provides an overview about the multi-target drug concept and discusses strategies to use the enormous pharmacological knowledge of natural products with privileged structures (i.e. curcumin, epigallocatechin-3-gallate, resveratrol, salicylate and quercetin) for developing anti-inflammatory multi-target drugs. Focus is placed on selecting molecular targets, judging their relevance and estimating safety concerns. An attractive aim might be to modulate natural product affinity to concrete but multiple molecular targets (based on the current knowledge of inflammation-relevant pathways) while maintaining their apparently beneficial broad target profile.

Introduction

Inflammation lies at the heart of many widespread diseases including rheumatoid arthritis, osteoarthritis, atherosclerosis, diabetes, neurodegeneration, allergy, infection and cancer [1]. Multiple signaling pathways form a network of pro-inflammatory, immunomodulatory and pro-resolving cascades, which define, by their interplay, the physiological and pathophysiological aspects of inflammation [1]. It becomes more and more evident that, for complex diseases like inflammation, an interference with multiple targets is superior to targeting a single key factor regarding drug efficiency, side-effects and adverse compensatory mechanisms [2].

Drug development during the past decades strongly focused on a limited number of key targets considered crucial for disease. Enormous efforts have been made to obtain potent and specific drugs, which shall combine high therapeutic efficacy with poor side-effect profile owing to the lack of off-target hits. Such a 'one-target-one-disease' approach led to the development of several valuable drugs [e.g. inhibitors of cyclooxygenase (COX) isoenzymes used for the therapy of inflammation, fever and pain] [3]. By contrast, this approach is restricted to a limited number of targets purely because their inhibition has to be sufficient to relieve or cure disease. To improve clinical efficacy, combination therapy is emerging. For example, intake of acetylsalicylic acid (aspirin) together with paracetamol (acetaminophen) and caffeine apparently relieves pain more efficiently than the single drugs [4]. However, there are three major drawbacks. First, patient compliance is reduced when multiple medications are prescribed, especially for the treatment of

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GLOSSARY

Arachidonic acid Major highly polyunsaturated ω-6 fatty acid of membrane phospholipids and precursor of eicosanoids.
Combination therapy Using more than one medication to treat a single disease, either by administrating separate or multi-component drugs.
Designed multiple ligands (DMLs) Multi-target compounds where biological profile has been rationally designed to improve efficacy or safety in the therapy of a particular disease.
Eicosanoids Metabolites of 20-carbon fatty acids (such as arachidonic acid) acting as local hormones via G-protein-coupled receptors and possessing pleiotropic physiological and pathophysiological functions primarily related to immunomodulation.
Multi-component drugs Dosage form that contains multiple pharmacologically active ingredients.
Multi-target drugs Compounds that have multiple but concrete molecular targets.
Natural product multi-target concept Extension of the multi-target concept that aims to exploit the profound pharmacological knowledge about natural medicine to select targets and leads for the design of multi-target drugs.
Nonsteroidal anti-inflammatory drugs (NSAIDs) Class of analgesic, antipyretic and anti-inflammatory drugs that interferes with eicosanoid biosynthesis and lacks the steroidal structure of glucocorticoids.
Privileged structures Molecular frameworks that can target a panel of different macromolecules upon structural modification.

asymptomatic and chronic diseases. Second, only explicit key targets associated with the respective disease are exploited but not the majority of disease-relevant signaling pathways. Thus, potential synergistic effects of inhibiting multiple pathways, perhaps only moderately to readjust homeostasis, remain unrevealed. Third, very complex pharmacokinetics might result, which make extensive clinical trials necessary to estimate benefit, side-effects and potential drug–drug interactions. Although the compliance issue can be resolved by combining individual drugs in a single pill (multi-component drugs), the others remain.

Although the benefits of interfering with multiple targets are unquestioned for complex diseases like inflammation, the polypharmacological strategy remains a matter of dispute. The potential of natural products from 'folk medicine' with often obscure mechanisms of action but proven (pre)clinical efficacy and safety has been widely neglected [5]. In the following, we present a multi-target concept (see Glossary) that exploits the broad but well-characterized target profile of structurally privileged natural leads. Advantages and disadvantages of this concept are discussed in light of the recent advances in the molecular pharmacology of the anti-inflammatory natural products curcumin, (−)-epigallocatechin-3-gallate (EGCG), *trans*-resveratrol, salicylic acid and quercetin (Fig. 1).

Inflammation and anti-inflammatory therapy

Inflammation is a complex (patho)physiological process, which is regulated by multiple signaling pathways, requires the interaction of different cell types and modulates a broad spectrum of cellular responses including immune cell maturation and function as well as tissue homeostasis [1]. Pharmacological strategies to suppress inflammation focus on agonists of the glucocorticoid receptor (glucocorticoids), interference with eicosanoid biosynthesis [nonsteroidal anti-inflammatory drugs (NSAIDs)] and the blockade of pro-inflammatory cytokine signaling [biologics targeting tumor necrosis factor (TNF)α and interleukin (IL)-1 signaling] [6]. Inhibitors of eicosanoid biosynthesis dominate among anti-inflammatory designed multiple ligands (DMLs; compounds with bioactivity profiles rationally designed to address a distinct disease) [2,7,8]. This preference is not surprising because eicosanoids are powerful lipid mediators with pleiotropic, often opposing, activities [9]. They combine pro-inflammatory, immunomodulatory, pro-resolving as well as homeostatic properties depending on structure, concentration and responsive tissue [9]. The specific interference with pro-inflammatory eicosanoid formation without affecting physiologically relevant levels of eicosanoids is therefore considered key to avoid side-effects. Strategies to achieve such a well balanced modulation of the eicosanoid profile focus on the selective inhibition of terminal isoenzymes of eicosanoid biosynthesis and on multi-target inhibitors [2,7,8].

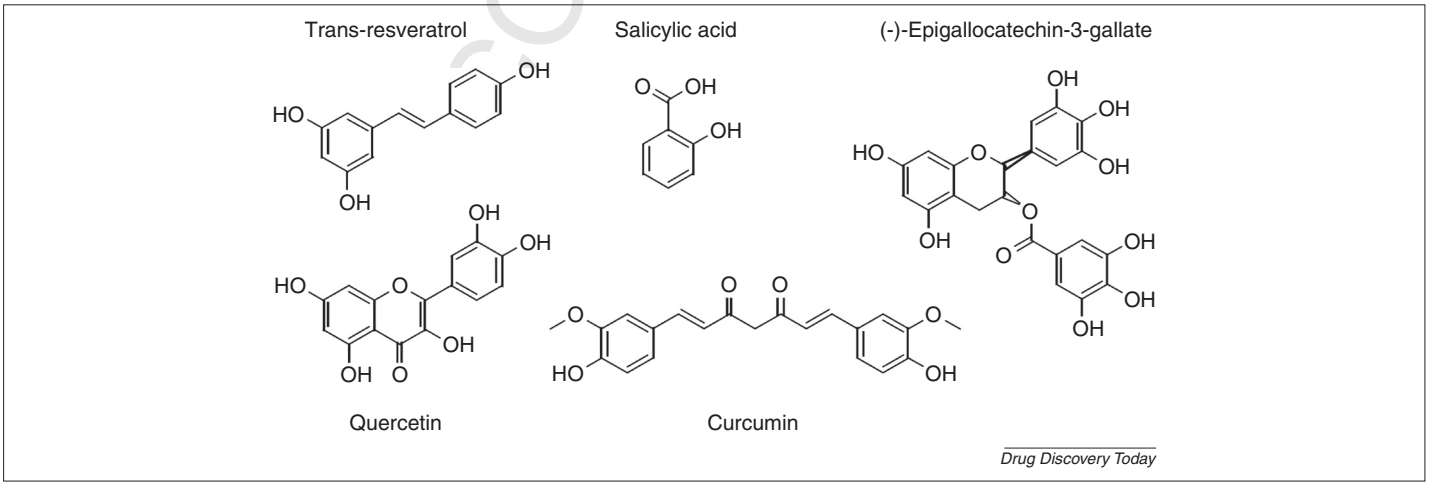

FIGURE 1

Structures of selected multi-target natural products.

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