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Review

Modulation of the Mas-Related G Protein-Coupled Receptor X2 (MRGPRX2) by Xenobiotic Compounds and Its Relevance to Human Diseases

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Abstract: Mast cells (MCs) are immune cells that reside in tissues; particularly in the skin, and in the gastrointestinal and respiratory tracts. In recent years, there has been considerable interest in the Mas-Related G Protein-Coupled Receptor X2 (MRGPRX2), which is present on the surface of MCs and can be targeted by multiple exogenous and endogenous ligands. It is potentially implicated in non-IgE-mediated pseudoallergic reactions and inflammatory conditions such as asthma or atopic dermatitis. In this paper, we review natural products and herbal medicines that may potentially interact with MRGPRX2. They mainly belong to the classes of polyphenols, flavonoids, coumarins, and alkaloids. Representative compounds include rosmarinic acid, liquiritin from licorice extract, osthole, and sinomenine, respectively. While evidence-based medicine studies are still required, these compounds have shown diverse effects, such as antioxidant, analgesic, anti-inflammatory, or neuroprotective. However, despite potential beneficial effects, their use is also burdened with risks of fatal reactions such as anaphylaxis. The role of MRGPRX2 in these reactions is a subject of debate. This review explores the literature on xenobiotic compounds from herbal medicines that have been shown to act as MRGPRX2 ligands, and their potential clinical significance.

Keywords: xenobiotic; MRGPRX2; mast cell; polyphenols; flavonoids; coumarins; alkaloids

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1. Introduction

Mast cells (MCs) are, among a number of other functions, the primary initiators of allergic and allergic-like symptoms; they swiftly release numerous mediators upon activation. Allergic MC activation occurs via an IgE-dependent pathway, in which the allergen is matched to a specific IgE that binds to a high-affinity IgE receptor (FcεRI) on the cell surface [1]. However, there are also clinical reactions that resemble allergy and develop after exposure to a variety of xenobiotic compounds for which IgE-mediated mechanisms have not been demonstrated and are therefore termed pseudoallergic or anaphylactoid [2]. After a period of uncertainty regarding the responsible pathway, the Mas-Related G Protein-Coupled Receptor X2 (MRGPRX2) was proposed to be one of the possible IgE-independent MC activation pathways [3]. McNeil et al. demonstrated that MRGPRX2 can be activated by xenobiotics, including fluoroquinolones, neuromuscular blocking agents, and peptidergic therapeutics (e.g., icatibant, leuprolide), in addition to previously known endogenous ligands such as neuropeptides and substance P (SP) [4]. Since the publication of McNeil's seminal paper in 2015, the number of publications addressing xenobiotic triggering of MRGPRX2 has increased rapidly. The hypothesis that drug hypersensitivity reactions are induced via an MRGPRX2-dependent pathway,

mainly by drugs from the muscle relaxant and flouroquinolone antibiotic groups, has attracted much attention from the scientific community [5]. However, many studies have also been devoted to other xenobiotics—including those found in medicinal plants—and these analyse their association with the MRGPRX2 receptor. In this article, we review these studies, focusing on the best documented evidence and the most representative compounds derived from the polyphenols, coumarins, alkaloids, and other groups that could have a potential impact on accelerating or alleviating MRGPRX2-dependent diseases. In addition to an analysis of the latest available data on the association of MRGPRX2 with xenobiotics and its potential clinical relevance, we also discuss the limitations of these studies, highlighting the current knowledge gap.

2. Pathophysiological Basis

2.1. Mast Cell Characteristics

MCs are immune cells that are present in almost all tissues of the body but are particularly abundant in those tissues directly exposed to the external environment [6]. While MCs are primarily associated with allergic reactions, they also play a significant role in various physiological and pathological processes [7–11].

All MCs contain intracellular granules and express the high-affinity IgE receptor FcεRI on their surface [12]. The cross-linking of FcεRI receptors upon antigen-IgE binding is the most recognized pathway of MC activation, playing a crucial role in potentially fatal reactions such as anaphylaxis [1]. MC stimulation leads to degranulation and the release of granule contents, which is a primary cause of hypersensitivity manifestations [1]. The granules store a wide range of preformed mediators, including histamine [13], proteases such as tryptases and chymases [13,14], and also some cytokines; mainly tumor necrosis factor alpha (TNF-α) [15]. These substances cause various biological effects, such as increasing vascular permeability, smooth muscle contraction and activation of immune cells, which are associated with symptoms of allergic inflammation [16]. In addition to the immediate release of preformed mediators, MCs also secrete de novo synthesized compounds that are produced after MC stimulation [13]. These include lipid mediators—such as prostaglandin D2 (PGD2), which are rapidly produced and released [17]—and cytokines, which are produced and secreted over a longer period of time (hours rather than minutes) [18–20].

In humans, MCs are generally categorized into one of three subtypes, based on the content of specific proteases. MCs that contain only tryptase (MC_T) are found in the mucosa of the small intestine and in the alveolar septa [21]. MCs that contain only chymase (MC_C) are commonly found in synovial tissue. MCs, which contain both tryptase and chymase (MC_{TC}), are predominantly found in the skin, submucosal layers of the small intestine, and tonsils [22]. However, at the transcriptional level, the protease content displays more tissue-specific variability, which is evident both between and within tissues [12]. Cutting-edge advancements in single-cell profiling technologies have opened new avenues to unravel the complexity and diversity of MCs. These breakthroughs shed light on previously unseen heterogeneity among MCs across various tissues, which is distinct from other cell types. In humans, transcriptomic analysis unveiled the existence of seven distinct MC subsets (MC1–7) distributed across 12 organs, each with unique transcriptomic core signatures [23].

All MCs express FcεRI, but there is controversy regarding whether MC_T and MC_C express MRGPRX2, despite the known expression of MRGPRX2 in skin MC_{TC} [24–26]. Furthermore, even among skin MC_{TC}, only a small percentage of cells exhibit MRGPRX2 expression under steady-state conditions [24,25].

2.2. Structure and Regulation of MRGPRX2 Function

MRGPRX2 is a G protein-coupled receptor (GPCR) that was first reported to be expressed mainly on MCs and sensory neurons [3,27]. The receptor has low affinity and low selectivity with respect to ligand binding. MRGPRX2 has been shown to be activated by a wide range of endogenous and exogenous compounds, primarily by small cationic molecules and peptides that have amphipathic properties, or share a motif of tetrahy-

droisoquinoline (THIQ) or a similar motif [4,5]. Endogenous ligands of MRGPRX2 include neuropeptides such as SP, PAMP-12, and cortistatin-14 (CST-14), as well as antimicrobial host defense peptides such as cathelicidin LL-37, hBD2, and eosinophil granule proteins (e.g., MBP). Exogenous ligands of MRGPRX2 include the cationic polymer compound 48/80 (C48/80), which is commonly used in receptor functional assays, and a variety of drugs approved by the Food and Drug Administration (FDA), such as fluoroquinolones (e.g., ciprofloxacin), neuromuscular blocking agents (e.g., rocuronium, atracurium), opioids (e.g., morphine), and many others [4,9,28]. MRGPRX2 can also be activated or inhibited by other exogenous agents, such as bacterial quorum sensing proteins, insect venoms [3,29,30], or many different plant xenobiotics (Figure 1) [31–59]; representatives of which are described in the following part of this review.

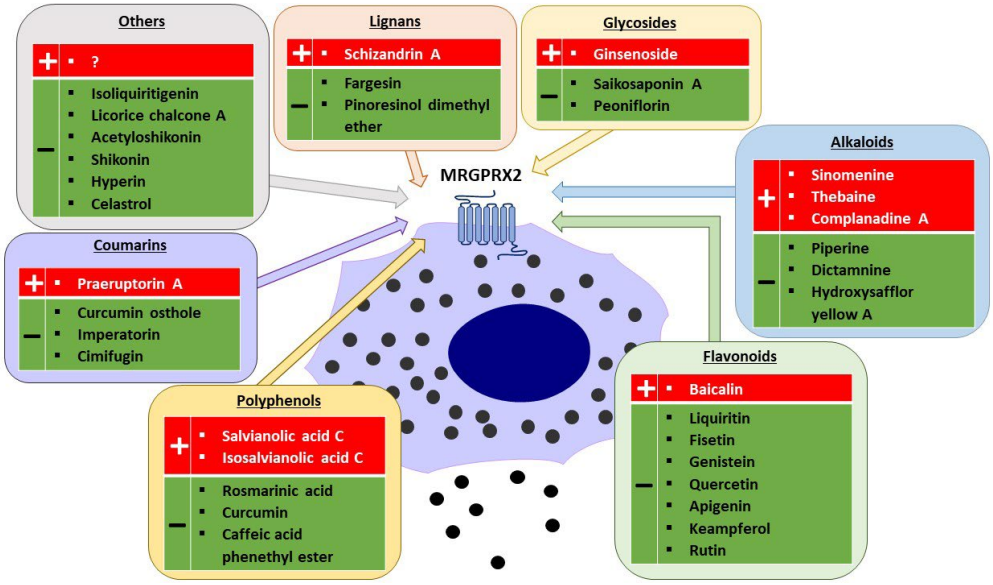

Figure 1. Plant-derived agonists (+) and inhibitors (−) of MRGPRX2 (created with Motifolio, Motifolio Inc., Elliocott City, MD, USA).

As a GPCR, MRGPRX2 shares the structure of seven transmembrane (TM) α-helices connected by three extracellular loops (ECLs) and three intracellular loops (ICLs) [60]. The ECL region contains the N-terminus responsible for ligand binding, whereas the ICL region contains the C-terminus involved in G protein coupling, β-arrestin recruitment, and downstream signalling [61–64]. The extracellular binding of ligands to MRGPRX2 promotes the conformational changes in the transmembrane domains, resulting in structural changes on the cytoplasmic side of the membrane and activation of G proteins, and subsequent MC degranulation [65]. Conversely, some ligands can induce intracellular β-arrestin recruitment, leading to receptor desensitization and internalization [62]. The downstream signalling pathways of MRGPRX2 involve the activation of the phospholipase C pathway (PLC-PKC-IP3R), which result in intracellular Ca^{2+} influx and MC degranulation. Additionally, the MAP kinase (ERK-P38-JNK), PI3K-AKT, and NF-κB pathways are activated, leading to cytokines and PGD2 synthesis in MCs [7].

2.3. Role of MRGPRX2 in MC-Driven Skin Diseases

To date, the exact role of MRGPRX2 in MCs has not been fully understood [9]. Numerous in vivo and in vitro studies have been conducted on the receptor (and its mouse ortholog, MrgprB2 [4]), indicating its potential involvement in various physiological and pathological processes. With its ability to bind to a diverse range of ligands, MRGPRX2 has been implicated in drug pseudoallergic reactions, neurogenic inflammation, and a wide array of inflammatory diseases such as allergic contact dermatitis (ACD), chronic urticaria (CU), rosacea, rheumatoid arthritis, atopic dermatitis (AD), mastocytosis, ulcerative

colitis, and allergic asthma [8–11]. However, conclusive evidence regarding MRGPRX2's involvement in these conditions in humans is still lacking.

Endogenous peptides considered to be MRGPRX2 ligand play an important role in the development of inflammatory skin diseases. The neuropeptide SP and the host defense peptide cathelicidin LL-37 are key players in the pathogenesis of rosacea and AD, and are upregulated in the skin of patients [8,10]. Both peptides in vitro were shown to activate MCs via MRGPRX2, leading to MC degranulation and release of pro-inflammatory mediators, including histamine and cytokines (i.e., TNFα) [66,67]. It was proposed that the released mediators can subsequently act on sensory neurons and vascular endothelial cells to promote neurogenic inflammation, resulting in itching, erythema, swelling, and pain that exacerbate disease symptoms [8,10]. In addition, MC-derived mediators recruit immune cells into the inflamed tissue and stimulate both neurons and immune cells (such as neutrophils) to secrete more SP and LL-37, which then could again activate MCs [8,10,11]. Similar mechanisms involving SP and MCs are also present in ACD and CU [8,10,68]. Another neuropeptide ligand of MRGPRX2 involved in the development of neurogenic skin inflammation, such as the non-histaminergic pruritus associated with ACD, is CST-14 [8,10,69–71]. The skin conditions are also characterized by elevated levels of proinflammatory cytokines such as IL-13 and IL-31 [72–74]. It is noteworthy that in all these diseases, except CU, an increased number of MCs has been reported in the skin of patients compared to healthy controls [8,10]. Additionally, the expression of MRGPRX on cutaneous MCs is higher in patients with CU [24]. Therefore, the involvement of MRGPRX2 in inflammatory skin diseases is suggested [8,10,11].

In several of these diseases, the usual treatment with antihistamines and other first-line drugs has been reported to be ineffective [75–77]. With the current generation of H1-antihistamines, sedation has become a minor concern, as the use up to fourfold normal doses are minimally or non-sedating [77–79]. However, due to incomplete efficacy in all patients, the search for other medications remains a priority.

3. Traditional Chinese Medicines and Plant-Derived Compounds

Traditional Chinese medicine (TCM) is a medical therapy system that has been practiced for millennia. It stands as one of the earliest forms of medical practice recorded in global history. Given their extensive use in China and many other countries, traditional Chinese medicines (TCMs) remain among the most commonly prescribed therapeutic agents worldwide [80]. TCMs often consist of natural herbal and other remedies tailored for specific conditions such as allergic or heart diseases [81,82]. Both the beneficial effects and side effects of TCMs may potentially be linked, at least in part, to the interaction of active compounds with the MRGPRX2 receptor.

3.1. TCM Compounds in Evidence-Based Medicine and Their Potential for Use in Humans

Evidence-based medicine (EBM) involves making medical management decisions, particularly therapeutic decisions, based on current scientific evidence that has been systematically and reliably verified [83]. EBM is widely accepted in modern medicine in most countries and is based on the results of high-quality clinical trials; typically randomized, double-blinded, and placebo-controlled trial. In contrast, evidence from case-control studies, followed by case reports or studies in animal models or in vitro, is of less importance [83]. Chinese medicine, including treatment with herbs and their constituents, has a fundamentally different approach to therapeutic decision-making. The approach is based on a long-standing tradition, there is a lack of well-designed, standardized and reproducible clinical trials to demonstrate the efficacy and safety of the therapeutic interventions used [84,85]. TCM studies receive an average low mean score of 1.25 on the Jadad scale which is used to assess the methodological quality of clinical trials; a maximum score of 5 indicates the best-quality study [86]. The quality of clinical trials in TCM is limited by several factors. These include batch-to-batch variation of investigational products, difficulty in preparing appropriate placebos for multicomponent herbal preparations, unclear ran-

domization rules, and the discrepancy between the standardized intervention required by EBM and the individual patient approach inherent in TCM [84]. Therefore, data obtained within the TCM context are major risk factors for bias and may limit the translatability of these findings to an evidence-based clinical context.

Although there is increasing evidence of the biological activity of many xenobiotic compounds used in TCM formulations, this evidence is mostly derived from animal or in vitro models that evaluate the effects of specific isolated compounds at concentrations that may not be biologically relevant or representative of therapeutically used extracts (refer to Table 1). For instance, baicalin was claimed to possess "anticancer" activities in non-small cell lung cancer, but these conclusions came from a study that assessed its effect on tumor growth and survival in a mouse model [87]. The design of this study suggests that "anticancer" property should be considered as antineoplastic activity (i.e., elimination of cancer cells). In another example concerning cancer the authors showed, through experiments on cell culture, that osthole inhibits proliferation of gastric cancer cells [88]. Molecular modelling methods were applied in another study to target signalling pathways involved in breast cancer development with molecules such as salvianolic acid C [89]. This is also research that is still distant from clinical applications. It should therefore be noted that often the properties of TCM substances refers to their effects in experiments conducted, as mentioned above, in vitro and such properties cannot be directly translated into the clinic until they have been proven though robust placebo-controlled trials. It should also be emphasized that a number of the substances described below have not been registered as medicinal products by the FDA and the European Medicines Agency [90,91]. In TCM, these substances are attributed with anti-inflammatory effects (osthole [92–97], flavonoids [98–100]); have been proposed for use in heart disease (salvianolic acid C [101,102]), rheumatoid arthritis (sinomenine [103]), cardiovascular disease, gastrointestinal and respiratory infections (baicalin [104]); however, they also have very broad and non-specific indications (liquiritin [105], praeruptorin A [106], piperine [107], rosmarinic acid [108]).

Clinical data on interventions based on MRGPRX2 inhibition are limited. However, it is worth noting that in-human studies are already underway. Following successful basic in vivo studies in mouse and dog models [109], two clinical trials have been initiated with an orally administered specific MRGPRX2 antagonist—the synthetic small molecule compound EP262—in the indications of chronic spontaneous urticaria and atopic dermatitis [110]. Both studies are double-blinded, placebo-controlled, and randomized; therefore, they are expected to provide reliable results on the efficacy of the studied molecule. The primary outcome measure for urticaria is the change in a patient-reported questionnaire assessing the number of hives and intensity of itch over seven consecutive days. In the atopic dermatitis study, the primary objective is to evaluate the safety and tolerability of EP262. The results of these studies are expected to provide valuable insight into the practical clinical relevance of blocking MCs degranulation in the MRGPRX2-dependent pathway.

3.2. Polyphenols

Polyphenols are a broad and complex category of chemical substances derived from plants. These components have at least one aromatic ring with one or more hydroxyl (OH) groups in their structure, and are categorized into several classes; of which flavonoids, phenolic acids, lignans, and stilbenes are the main groups [111]. Polyphenols are commonly found in fruits and vegetables [111]. Few randomized clinical trials have demonstrated antioxidant, antidiabetic, and cardioprotective activity of some polyphenols, or their role in improvement of gut microbial composition as prebiotics [112–119]. Additionally, these are suggested to display many other biological effects such as anti-aging, anti-inflammatory, anticarcinogenic, and neuroprotective. However, direct in-human evidence on these alleged properties are so far lacking [111]. Several polyphenols have been reported as potential MRGPRX2 ligands exerting possible protective or pathological effects in chronic skin diseases and other conditions, including MRGPRX2-dependent pseudoallergy reactions [33,35,37,120].

3.2.1. Salvanolic Acid C and Isosalvanolic Acid C

Danshen injection (DI) is a traditional Chinese medicine injection solution (TCMI), containing the primary component derived from *Salvia miltiorrhi* [37,120]. It is commonly used in the medical treatment of angina pectoris [102], liver cirrhosis [121], and heart diseases including acute coronary syndrome [122]. However, the use of DI is often associated with adverse reactions, including anaphylaxis [123,124]. Three phenolic acids of *Salvia miltiorrhi*—namely salvianolic acid A (SA), salvianolic acid C (SC), and isosalvianolic acid C (ISC) (Figure 2)—have been identified as MRGPRX2 agonists and have been shown to induce degranulation of MCs [37,120]. Among them, SC was shown to exhibit the most potent MC stimulating activity. In the intracellular Ca^{2+} mobilization assay on MRGPRX2-transfected human embryonic kidney 293 (MRGPRX2-HEK293) cells, a half maximal effective concentration (EC_{50}) of the components was determined. The EC_{50} of SC, ISC and SA were 15.70 ± 4.62, 38.88 ± 8.67, and 363.40 ± 34.51 μM, respectively [37]. These results were confirmed by cell membrane chromatography, which showed that SC had the longest retention time on the column with MRGPRX2, indicating the strongest interaction with the receptor [37]. The authors also suggested that these polyphenolic compounds compete to bind to the active site of MRGPRX2 with ciprofloxacin, which is a known receptor ligand [37]. Molecular docking of ISC subsequently supported this hypothesis, showing that ISC forms at least three hydrogen bonds with MRGPRX2 in the active pocket [120]. In a mouse model of passive cutaneous anaphylaxis (PCA), the injection of SC and ISC into the mouse hind paw resulted in tissue swelling and increase of vascular permeability [37]; whereas hind paw inflammation was significantly inhibited in MrgprB2 knockout mice or mice with MCs depletion [120]. Furthermore, the activation and degranulation of Laboratory of Allergic Disease 2 (LAD2) human mast cells induced by SC and ISC was abolished in MRGPRX2 knockout cells [37,120]. These reports suggest that the polyphenolic compounds found in DI may be responsible for anaphylactoid reactions to the drug, especially two geometric isomers, SC and ISC. It is noteworthy that DI research has demonstrated the instability of SA in distilled water solutions, resulting in its conversion to SC and ISC, which are the more potent components [125]. However, the complex composition of DI does not exclude the involvement of other substances in the induction of the anaphylactoid reactions [124,126]. Similarly, the administration route, including the high dose of DI, which was described as the cause of some adverse drug reactions (ADRs) [127,128], could be the reason for allergy-like reactions to DI. The data highlight the need for caution in the administration of TCMI and the urgent need for in-depth research of TCMs ingredients.

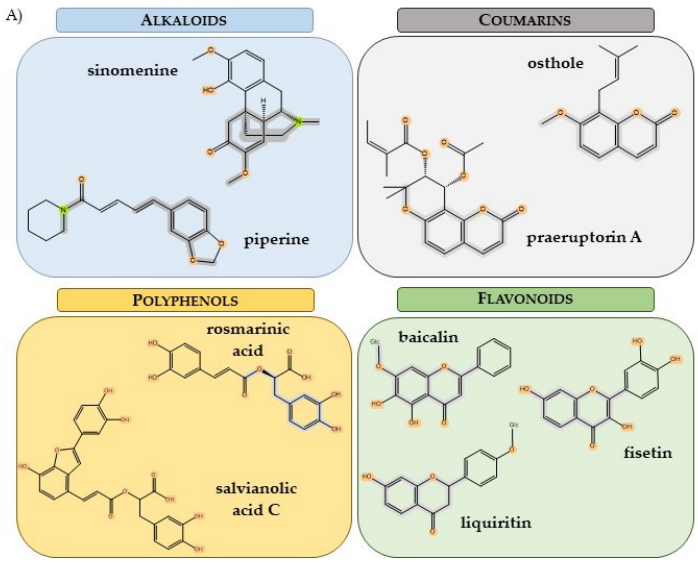

Figure 2. *Cont.*

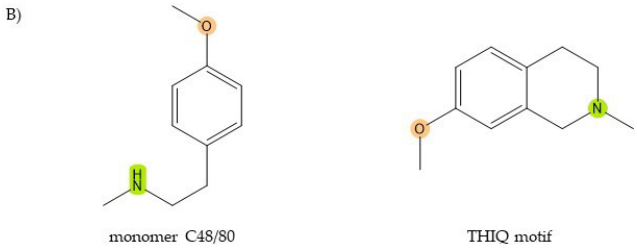

Figure 2. (**A**) Structure diagrams of selected compounds in the different ligand groups. (**B**) Two potent mast cell degranulators: monomer C48/80 and tetrahydroisoquinoline (THIQ) motif. Molecular fragments with patterns similar to monomer of C48/80 as well as heterocyclic motifs from THIQ are highlighted (created with ChemOffice 22.0, Perkin Elmer, Shelton, CT, USA).

3.2.2. Rosmarinic Acid

Rosmarinic acid (Figure 2) is a polyphenolic compound commonly found in *Rosemarinus officinalis*, popularly known as rosemary, and in other herbs, such as *Perilla frutescens*, which is widely used in TCM [108]. In vitro studies and animal models suggest that rosmarinic acid can have some physiological effects, including anti-inflammatory and antinociceptive activities (Table 1) [129,130]. One of its proposed mechanisms of action is the targeting of signalling pathway proteins, such as NF-κB [131]. Recently, data have emerged suggesting an ameliorative effect of rosmarinic acid on ACD and inhibition of MRGPRX2-mediated pseudoallergic reactions [35,72]. Ding et al. established a mouse model of dibutyl square acid-induced ACD that exhibits common symptoms of ACD, such as epidermal thickness, lymphocyte infiltration, MC degranulation, elevated serum levels of histamine and IL-13, and increased bouts of scratching in mice [72]. Notably, rosmarinic acid treatment reduced all symptoms of ACD in the mouse model. Furthermore, the ACD model exhibited increased expression of CST-14 mRNA, which was significantly decreased after administration of rosmarinic acid. The role of rosmarinic acid in MRGPRX2-mediated MC activation was also investigated. The results showed that pretreatment with rosmarinic acid reduced intracellular Ca^{2+} influx, LAD2 cell degranulation, and histamine release induced by CST-14 and C48/80 [35,72]. Furthermore, in cells treated with rosmarinic acid, MRGPRX2 mRNA and protein levels were downregulated whereas CST-14 expression levels remained unchanged [72]. The suppressing effect of rosmarinic acid on MC stimulation was also demonstrated to inhibit the activation of downstream signalling pathways. The compound decreased the phosphorylation of proteins associated with MC degranulation (PLC and IP3) and cytokine production (PKC and ERK), as well as NF-κB; this is consistent with previous studies [131]. Interestingly, the authors also performed a molecular docking study, in which they demonstrated that rosmarinic acid interacts with MRGPRX2 and associates with its G proteins at the intracellular site (Figure 3) [72]. Conversely, another study [40] indicated that rosmarinic acid is a weak inhibitor (IC_{50} = 1.8 mM) of C48/80-induced activation of MCs. However, the study was conducted in other cell lines, namely primary cell culture of mouse peritoneal mast cells (MPMC) and MRGPRX2-HEK293 cells, and the concentration of rosmarinic acid used in the study were significantly lower (10 μM versus 25–100 μM in the previous studies), which could have a big impact on data results. Additionally, the study did not provide additional evidence supporting weak performance of rosmarinic acid on MC activation [40]. On the other hand, the authors also performed molecular docking and showed that rosmarinic acid was not expected to interact with the MRGPRX2 binding pocket [40]. In conclusion, additional studies should be conducted to elucidate the effect of rosmarinic acid on MRGPRX2-mediated MC functions.

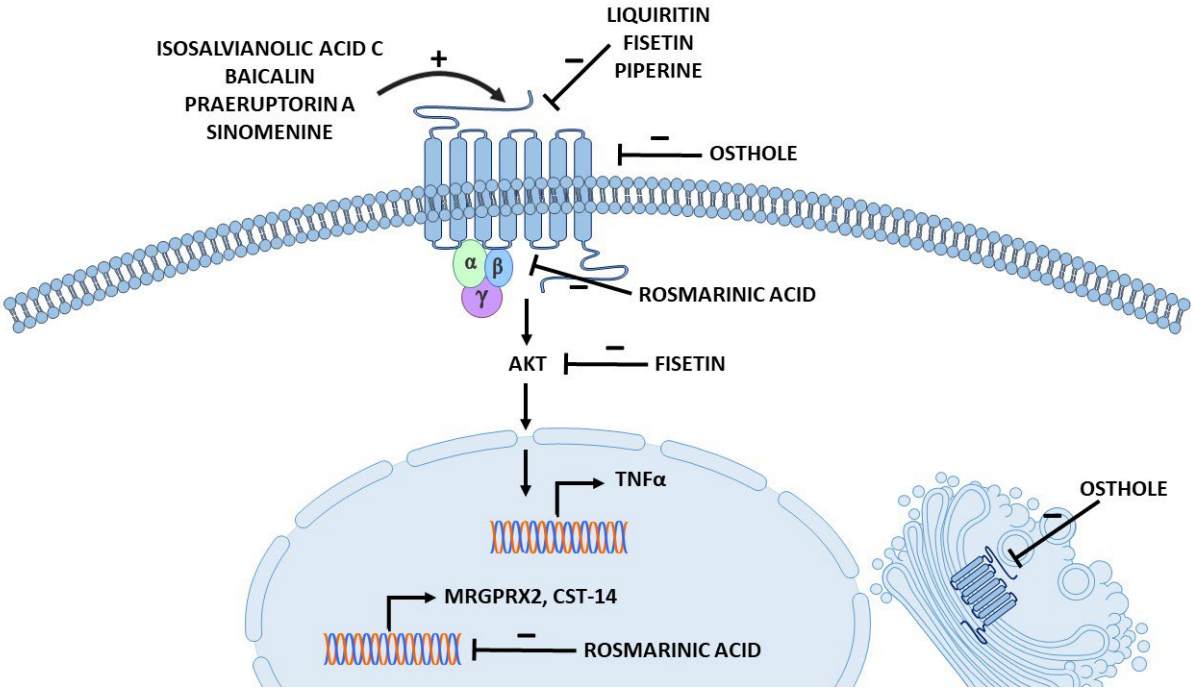

Figure 3. Proposed action points for different compounds affecting MRGPRX2 (created with Motifolio Inc., Elliocott City, MD, USA).

3.3. Flavonoids

Flavonoids are a large group of plant compounds—i.e., a subgroup of polyphenols—with a wide range of beneficial effects on human health [98]. They are very abundant in plants, including fruits and seeds; and contribute to their characteristics such as color, fragrance, and flavor [98]. Flavonoids have been reported to potentially exert biological activities such as anti-inflammatory, immunomodulatory, antibacterial, antiparasitic, antiviral, anticancer, anti-aging, neuroprotective, cardioprotective, and antidiabetic effects [98]. Several flavonoids have been identified as potential MRGPRX2 antagonists (Figure 1). Most of them have been reported to have protective effects against hypersensitivity reactions and other health conditions such as pruritus [56] or CU [42,132]. Additionally, agonists of MRGPRX2 among flavonoids have also been identified [33,133]. Flavonoids have been reported to affect MC stimulation both by direct binding to the receptor and by interactions with regulatory enzymes or transcription factors [42,132,134,135]. In this section, we describe a few representatives of flavonoids that may interact directly with MRGPRX2.

3.3.1. Baicalin

Baicalin, a flavone (Figure 2), is one of the major components of *Scutellaria baicalensis* Georgi, which is extracted from a dried root of the plant [33]. Baicalin is commonly used in TCMI for the treatment of inflammation, cardiovascular disease, and gastrointestinal and respiratory infections [104]. Although baicalin has multiple beneficial pharmacological activities (Table 1), TCMI with baicalin as the main active ingredient have been reported to induce a number of allergic reactions [67,136–139]. Therefore, Wang et al. investigated the role of baicalin in anaphylactoid reactions in mice [33]. Using mouse models of systemic and cutaneous anaphylaxis in wild type (WT) and MrgprB2 knockdown mice, the authors showed that baicalin induces receptor-dependent pseudoallergy [33]. Another study [133] demonstrated that this compound induces intracellular Ca^{2+} mobilization and histamine release in LAD2 cells, but not in MRGPRX2 knockdown LAD2 cells. Taken together, these data suggest that baicalin may induce anaphylactoid reactions to TCMI through MRGPRX2.

3.3.2. Liquiritin from Licorice Extract

Licorice (synonyms: liquorice, and Gan-Cao in Chinese [139]) is scientifically known as the genus *Glycyrrhiza* [105] and is widely used in the food industry (as flavoring and sweetener agents [31]), in cosmetics and in pharmaceuticals [105]. At the same time, licorice is one of the most widely used ingredients in TCM [31]. It has many alleged biological effects, including protective activities against many types of cancer [105], antibacterial and anti-inflammatory effects [105]. Licorice extract contains a wide range of bioactive components, including flavonoids such as liquiritin, chalconoids (isoliquiritigenin and licochalcon A), and saponins (glycyrrhizic acid) (Figure 1) [31,41,52,105]. Recent studies have proposed licorice ingredients as treatment agents for MRGPRX2-mediated anaphylactoid reactions [31,41,52]. In vitro studies of one of the active licorice flavonoids, liquiritin (LQ), demonstrated suppression of MC activation (intracellular Ca^{2+} mobilization assay) and degranulation (β-hexosaminidase and histamine release) [41]. The compound also showed an in vivo protective effect against anaphylaxis. In the mouse model of PCA, LQ injection into the hind paw resulted in a dose-dependent suppression of swelling and vasodilation and caused a reduction in the percentage of degranulated skin MCs [41]. The flavonoid also reduced histamine and inflammatory cytokines levels in the paw and serum of mice [41]. Liquiritin has been demonstrated to bind directly to MRGPRX2, and molecular docking studies indicate that it fits well into the active site of the receptor (Figure 3) [41]. At the same time, the compound showed low cytotoxicity in tested cells and no activating effect on MCs [41]. However, it is worth noting that the study did not include MrgprB2 knockout mice or MRGPRX2 silencing, which constitutes a limitation. Nonetheless, these results suggest that LQ may be a potential MRGPRX2 inhibitor and provide a basis for further research.

3.3.3. Fisetin

Another natural flavonoid that possesses a range of potential health-related bioactive properties is fisetin (Figure 2). Fisetin is found in various fruits and vegetables [140,141] and has been proposed to have anti-inflammatory [99] and antiallergic effects (Table 1) [100]. It has been reported to inhibit several signalling pathways in vitro, including PI3K-Akt-mTOR, P38, and NF-κB [142,143], which were associated with an inhibitory effect in human inflammatory skin models [144]. Recent research on the SP and ovalbumin co-stimulated CU mouse model demonstrated protective effects of fisetin against CU [42]. The compound alleviated the symptoms associated with CU in mice and reduced serum levels of inflammatory mediators such as histamine and TNFα, as well as the infiltration of red blood cells into the tissue and degranulation of skin MCs [42]. Additionally, fisetin suppressed local and systemic anaphylactoid reactions in mice [42]. The study revealed that fisetin exerts its inhibitory effects by binding to the active site of MRGPRX2, thus preventing MCs activation [42]. Fisetin also targets the AKT signalling molecule, which is consistent with previous reports on inhibition of signalling pathways (Figure 3) [142–144]. In conclusion, fisetin can be considered as a potential MRGPRX2 antagonist in future research.

3.4. Coumarins

Coumarins are secondary metabolites that belong to the benzopyrone family and are commonly found in many plants [145]. They were shown to potentially exhibit a range of pharmacological activities, including anti-inflammatory [146,147], antibacterial, antiviral, antifungal [148], anticancer [149], antihypertensive [145], antioxidant [150], and neuroprotective effects [145]. To date, hundreds of coumarins have been identified and described [145,151]. Here, we present representative examples of coumarins that affect the response of MCs via MRGPRX2 signalling.

3.4.1. Praeruptorin A

Praeruptorins are bioactive coumarins extracted from *Peucedanum* species such as *P. praeruptorum*, which are widely used in TCM [106]. Praeruptorins have many beneficial

physiological effects in the treatment of upper respiratory tract infections, cardiovascular, immune, and nervous system diseases [106]. One of these biological compounds is praeruptorin A, which exhibits several bioactive properties (Table 1) and has been studied in the context of MC activation via MRGPRX2 [38]. A competitive binding assay showed that this compound competes with ciprofloxacin for binding to MRGPRX2, suggesting that it may interact directly with the receptor [38]. Stimulation of LAD2 cells by praeruptorin A caused β-hexosaminidase and histamine release [38], suggesting that this compound may trigger MRGPRX2-mediated pseudoallergy reactions; however, the data are very limited and thus further studies are required.

3.4.2. Osthole

Osthole is a coumarin extracted from the dried fruits of the *Cnidium monnieri* Cusson plant (Figure 2). It is used in TCM to treat various pathological conditions. Osthole has been considered to possess anti-inflammatory properties [92,93] and has been shown to have protective effects in animal models of allergic asthma [94,95] and AD [97] (Table 1). The study by Callahan et al. [34] demonstrated that osthole attenuated both the early and late phases of MC activation and allergic inflammation in mice in vivo. The compound significantly reduced intracellular Ca^{2+} mobilization and MC degranulation induced by known MRGPRX2 ligands: SP, C48/80, and LL-37. MCs treated with osthole showed a reduction in cytokine release after MC activation and a significant downregulation of kinases phosphorylation in the downstream signalling pathway [34]. Moreover, in the mouse models of PCA and chronic skin rosacea, osthole attenuated the inflammatory response to C48/80 or LL-37 injection, respectively [34]. The compound reduced mRNA levels of MC inflammatory mediators, the percentage of degranulated MCs; and decreased redness, epidermal thickness, and cellular infiltration in the skin of the treated mice cohort [34]. The authors showed that osthole inhibits MC activation through allosteric rather than competitive interactions with MRGPRX2 (Figure 3) [34]. Furthermore, this study showed that osthole affects both the surface and intracellular expression levels of MRGPRX2, providing another possible way to regulate the MRGPRX2 response in allergic reactions and rosacea [34]. However, another study showed that osthole could induce degranulation in rat basophilic leukemia (RBL-2H3) cells, which have rat homologue of MRGPRX2; MrgprB3, and FcεRI [38]. The authors imply the interaction of osthole with IgE receptor, due to results of competitive binding assay with quercetin (used as ligand of FcεRI in the assay). However, in a later study quercetin has been reported to inhibit MRGPRX2 and MrgprB2 by direct binding [46]. Therefore, due to insufficient data, the conclusions should be drawn carefully.

3.5. Alkaloids

Alkaloids are plant and animal metabolites that comprise a wide range of compounds that share nitrogen as a characteristic chemical element present in their structures. As a result of their structural diversity, alkaloids have numerous biological properties and are widely used in modern medicine. Illustrative applications of alkaloids in healthcare include chemotherapy (paclitaxel, vinblastine), analgesics (morphine, codeine), treatment of respiratory diseases (codeine, capsaicin), dietary supplements (piperine), and many others [152]. The classification of plant alkaloids is based on their chemical structure, biochemical precursors, and their occurrence in different plant genera. Here, we describe two alkaloids with opposite effects on MRGPRX2-dependent MC activation, namely sinomenine and piperine, which belong to the opium and piperidine alkaloids, respectively [152].

3.5.1. Sinomenine

Natural opium alkaloids (such as codeine, morphine, and its derivatives such as sinomenine, thebaine, pethidine, etc.) have been extensively described as MRGPRX2 agonists [4,32,39,153]. Sinomenine (Figure 2) is extracted from the root of the medicinal plant *Caulis sinomenii* and is a major active component of TCMI, used to treat rheumatoid arthritis [103,154]. Some studies have confirmed the interaction of sinomenine and MRGPRX2

on MC lines, suggesting a possible contribution of MRGPRX2 in sinomenine anaphylactoid reactions [32,39,153,155]. Liu et al. showed that sinomenine increased intracellular Ca^{2+} influx in LAD2 cells and MPMC [153]. However, the response was significantly reduced in MRGPRX2/MrgprB2 silenced cells [153]. Depletion of MRGPRX2 in LAD2 cells was also associated with the absence of sinomenine-induced degranulation as assessed by β-hexosaminidase and histamine release. Treatment of LAD2 cells with sinomenine for 24 h induced a significant upregulation of MC cytokine expression and secretion, as well as MRGPRX2 protein level in the cells and the phosphorylation levels of signalling pathway proteins (PLC, IP3R, P38, PKC). These responses were significantly reduced in MRGPRX2 knockdown LAD2 cells [153]. The anaphylactic effect of sinomenine in vivo was also investigated. The mouse model of PCA showed that sinomenine injection induced extensive paw extravasation and swelling. These inflammatory responses were almost completely absent in mice with MC depletion or MrgprB2 knockdown mice, compared to WT mice [153]. Molecular docking and competitive binding studies showed that sinomenine binds directly to MRGPRX2 [155], most likely at the active site of the receptor (Figure 3) [39,153]. These studies have also determined EC_{50} for sinomenine. For LAD2 cells, EC_{50} was 2.16 μM [32], for MRGPRX2-HEK293 cells it was 1.84 μM and 2.77 ± 0.44 μM ([32] and [153], respectively), and for MrgprB2-HEK293 cells it was 2318 ± 314 μM [153]. The data showed the EC_{50} values to be even lower than those obtained for morphine and MRGPRX2 (4.5–7 μM) [39,156,157].

3.5.2. Piperine

Piperine is another alkaloid with inhibitory properties related to MRGPRX2 [36]. It is found in the fruits of long and black peppers (*Piper longum* and *Piper nigrum*) [152]. Piperine has been reported to suppress both early (degranulation) and late (de novo synthesis of mediators) responses to MC activation [36]. In addition to inhibiting C48/80-induced LAD2 cells degranulation, it also reduced ciprofloxacin and LL-37-induced activation of MCs [36]. Additionally, affinity chromatography methods showed a competitive binding of piperine to MRGPRX2 compared to sinomenine and ciprofloxacin [36,38]. In animal models, piperine ameliorated cutaneous symptoms and systemic anaphylaxis in mice [36]. Piperine could also reduce secretion of IL-31, suggesting that it has alleviating effect on pruritus [36,73]. In addition, the suppressive effect on MC degranulation induced by LL-37 [36], which is abundant in rosacea tissues [8,10], highlights the potential use of piperine in the treatment of this condition. In conclusion, these data indicate that piperine exhibits certain inhibitory properties related to the attenuation of the MC simulation, including drug-induced MC activation leading to allergic reactions. Therefore, further studies are warranted to elucidate its potential as a therapeutic agent in allergic conditions.

Table 1. Overview of compounds discussed in this manuscript (further details of the experimental studies are presented in the Supplementary Materials—Table S1).

Compound	Experimental Model or Methods	Primary Outcome Measure	Key Conclusions about Compound Activity	References	MRGPRX2 Inhibition and/or Activation	EC_{50} and/or IC_{50} for MRGPRX2 (Experimental Model and Assay)	C_{max} in Plasma
Salvianolic acid	Molecular docking, molecular dynamics	Inhibition of PI3K and mTOR	A candidate for in vitro experiments in breast cancer studies	[89]	Activation * [37]	EC_{50} = 15.70 ± 4.62 μM (MPMC, β-hexosaminidase release assay) [37]	171.48 ± 9.42 ng/mL [1] (0.00024 μM) [158]
Rosmarinic acid	Mouse and rat models	Behavioral tests	Antinociceptive and anti-inflammatory activity	[130]	Inhibition [72] /no effect [35,40] [2]	IC_{50} = 1.8 mM (MRGPRX2-HEK293 cells, retention time on CMC column) [40] IC_{50} cannot be calculated (MRGPRX2-HEK293 cells, intracellular Ca^{2+} mobilization assay) [35]	162.20 ± 40.20 nmol/L (0.162 mM) [160]
	Carrageenan-induced pleurisy and paw edema tests in rats	Behavioral tests	Potential for anti-inflammatory and antinociceptive activity	[129]			
	PC12 cells	Amyloid β-induced cellular reactive oxygen species generation	A candidate for neuroprotective treatment of Alzheimer's disease	[159]			
	Mouse model of cardiac fibrosis	Morphological examination, echocardiography	Promising as a therapeutic agent against cardiac fibrosis	[161]			
Baicalin	Mouse model of anxiety/depression	Depression-like behaviors	Improvement of anxiety/depression-like behaviors	[162]	Activation * [33,133]	NA	-
	Rat model of peridontitis	Toll-like receptor expression	Potential for treatment of periodontitis	[163]			
	Mouse model	Tumor growth	Potential for treatment of lung cancer	[87]			
Liquiritin	Rat model	Cell viability, inflammatory cytokine expression	Beneficial impact on pressure ulcers	[164]	Inhibition [41]	NA	-
	Rat model	Behavioral tests	Potential for treatment of bone cancer pain	[165]			
	PC12 cells	Expression of proteins involved in signalling pathway	Neuroprotective activity	[166]			
	Diabetic mouse model	α-glucosidase inhibition	Potential for treating diabetes	[167]			
	H9C2 cells	Cell viability level	Cardioprotective effect	[168]			
Fisetin	Male C57bl/6 J mice	Histopathological and serological injury markers	Protection against septic acute kidney injury	[142]	Inhibition [42]	NA	-
	Prostate and lung adenocarcinoma cells	Inhibition of the PI3K/AKT and the mTOR pathways	Potential as adjuvant with chemotherapeutic drugs	[143]			

Table 1. *Cont.*

Compound	Experimental Model or Methods	Primary Outcome Measure	Key Conclusions about Compound Activity	References	MRGPRX2 Inhibition and/or Activation	EC_{50} and/or IC_{50} for MRGPRX2 (Experimental Model and Assay)	C_{max} in Plasma
Osthole	Pulmonary inflammation induced in mice	Inflammatory parameters in BAL fluid	Potential for inhibition of inflammation in chronic obstructive pulmonary disease	[169]	Inhibition [34]/ activation [38] [3]	NA	-
	Mouse model	Itch–scratch response	Antipruritic activity	[170]			
	Mouse monocyte-macrophage cells	Inflammatory mediators' level	Potential for treatment of ulcerative colitis	[92]			
	Model of middle cerebral artery occlusion in rats	Determination of the infarct area	Potential for neuroprotective therapy in ischemic stroke	[93]			
	Bleomycin induced pulmonary fibrosis in rats	Expression of inflammatory mediators	Beneficial effects in tested model	[171]			
	Cervical cancer cell lines	Cancer cell viability, proliferation, and migration and invasion	Potential as adjuvant treatment for cervical cancer	[172]			
	Human gastric cancer cells	Cell proliferation and apoptosis	Potential for inhibition of gastric cancer cells proliferation	[88]			
	Osteosarcoma cell lines	Cell viability	Potential for osteosarcoma treatment	[173]			
	Tumor-bearing mice	Survival days	Potential for developing antitumor drugs	[174]			
	Diabetic mice	PPAR activation	Potential for treatment of diabetes	[175]			
	Skeletal muscle cells	Expression of AMP-activated protein kinase and glucose transporter 4	Potential for treatment of diabetes	[176]			
Praerup-torin A	Mouse macrophages	Expression of NF-κB-related proteins	Potential as a drug for viral infection	[177]	Activation [38]	NA	-
	Human hepatocellular carcinoma	Migration and invasion of tested cells	Potential as a therapeutic agent in human hepatocellular carcinoma	[178]			
Sinomenine	Rat neuron–glial cultures	Expression of TNF-α, prostaglandin E2, and reactive oxygen species	Potential for treatment of inflammation-mediated neuro-degenerative diseases	[179]	Activation [32,39,43,153,155]	EC_{50} = 2.16 μM (LAD2 cells, intracellular Ca^{2+} mobilization assay) [32] EC_{50} = 1.84 μM (MRGPRX2-HEK293 cells, intracellular Ca^{2+} mobilization assay) [32] EC_{50} = 2.77 ± 0.44 μM (MRGPRX2-HEK293 cells, intracellular Ca^{2+} mobilization assay) [153] EC_{50} = 2318 ± 314 μM (MrgprB2-HEK293 cells, intracellular Ca^{2+} mobilization assay) [153]	123 ± 22 ng/mL (0.00037 μM) [181]
	Rats and mice models	Behavioral tests	Analgesic effect in rodent models	[180]			
	Human bladder cancer cell line	P-glycoprotein expression	A candidate for treatment of bladder cancer	[182]			
	Mouse model of middle cerebral artery occlusion	Brain edema, neuronal apoptosis, neurological deficiency	A candidate for stroke therapy	[183]			
	Microglial cells	Amyloid β-induced levels of reactive oxygen species and nitric oxide	Potential for treatment of Alzheimer's diseases	[184]			

Table 1. *Cont.*

Compound	Experimental Model or Methods	Primary Outcome Measure	Key Conclusions about Compound Activity	References	MRGPRX2 Inhibition and/or Activation	EC_{50} and/or IC_{50} for MRGPRX2 (Experimental Model and Assay)	C_{max} in Plasma
Piperine	Cervical cancer and non-tumoral cell lines	Cell proliferation, viability, and migration	Potential as complementary treatment in cervical cancer	[185]	Inhibition [36,38]	NA	-

* For these compounds reports of anaphylactoid reactions to injections with them are cited in the main text. [1] Maximum concentration in rat plasma. [2] Rosmarinic acid has been described in separate studies as inhibitory compound for MRGPRX2 or with no effect on the receptor; for details see Section 3.2.2. [3] Osthole has been described as an inhibitory compound for MRGPRX2 and an activator of RBL-2H3 cells with unclear target; for details see Section 3.4.2. Abbreviations: BAL, bronchoalveolar lavage; C_{max}, maximum concentration in plasma; EC_{50}, half maximal effective concentration; IC_{50}, half maximal inhibitory concentration; MPMC, mouse peritoneal mast cells; mTOR, mammalian target of rapamycin; NA, not applicable; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; PI3K, phosphoinositide 3-kinase; PPAR, peroxisome proliferator-activated receptors; TNF, tumor necrosis factor.

4. Discussion

In vitro and in vivo studies using animals have demonstrated the involvement of the MRGPRX2 receptor on MCs in numerous physiological and pathological processes—including anaphylactoid responses to various ligands—including FDA-approved drugs, immune responses, host defense against bacteria, tissue homeostasis and repair, nociception and pain, and sleep regulation [11,186]. However, there is a lack of reliable studies in humans. MRGPRX2 is known to be activated by a variety of naturally derived ligands, including phenols, terpenoids, flavonoids, quinones, coumarins, and lignans, as highlighted in the recent literature [9,10]. A wide range of these compounds are used in TCM for the prevention and treatment of various diseases [187]. It should be noted that the estimated number of TCMs is around 12,800 [188]. Despite the increasing use of TCMs worldwide and their therapeutic appeal, its integration into mainstream healthcare continues to be impeded by the absence of strong evidence from an evidence-based medicine (EBM) standpoint. One fundamental limitation is the batch-to-batch variation of the active constituents contained in the herbal formulation used [84].

Nevertheless, TCMs injections are widely used in clinical settings; but ADRs, including the incidence of anaphylaxis, have been increasing annually, posing a serious public health concern [189]. On the other hand, TCM components and other herbal substances have been reported to have an inhibitory effect on MRGPRX2-induced MC stimulation and have been suggested to have protective effects in many skin diseases and pseudoallergic reactions (Figure 1) [9]. Notably, flavonoids, which are typically known for their anti-inflammatory properties (Table 1), exhibit diverse effects on MRGPRX2. Baicalein, for instance, is an exception that can cause pseudoallergic reactions by activating MRGPRX2 [9]; while other flavonoids, which are richer in hydroxyl groups, act as antagonists of this receptor. The most prominent group of the receptor agonists are the opium alkaloids, which include morphine, codeine, sinomenine, and thebaine [4,32,39]. Given that some of these compounds are present in TCMs and have been described to cause anaphylactoid reactions, as have a large number of drugs approved by the FDA, it is important to be aware of the possibility of their occurrence and to manage them appropriately.

On the other hand, some TCM compounds were reported to indicate protective effects against MRGPRX2-dependent anaphylaxis and chronic skin disorders. For instance, one of the candidates could be osthole, a plant-derived coumarin, which has been shown to reduce SP- and LL-37-induced MC degranulation, and to attenuate mouse models of anaphylaxis to SP and LL-37-stimulated rosacea [34]. Similar results were obtained with piperine, which also prevented MCs degranulation to LL-37, but also reduced IL-31 secretion [36], which has been proposed as a key clinical target for the treatment of pruritus [73]. Treatment with fisetin abolished the SP and ovalbumin co-stimulated mouse model of CU [42]. In the mouse model of ACD, rosmarinic acid has been demonstrated to attenuate ACD manifestations and suppress non-histaminergic pruritus by inhibiting MRGPRX2-mediated MC degranulation to CST-14 and by reducing levels of the proinflammatory cytokine IL-13 in mouse tissues [72,74]. In addition, rosmarinic acid and osthole act on the level of MRGPRX2 in the MC, therefore they may have additional suppressing effects in pseudoallergic reactions and skin diseases [34,72].

There are several limitations in the studies presented in this review. All data are based on preclinical studies involving cell lines and mouse models. While animal models with knockdown of MrgprB2, along with in vitro studies using human cell lines and MRGPRX2 knockdown/silencing, have demonstrated the involvement of the aforementioned xenobiotics in MRGPRX2-mediated MC activation/inhibition, conclusive evidence is still needed to confirm whether MRGPRX2 can mediate such effects in humans. While evolutionarily conserved, differences exist between human and mouse MCs. Human MCs demonstrate higher diversity, and the expression of MRGPRX2 can significantly vary among individuals. [23,190] Moreover, there is only approximately 53% overall sequence similarity between mouse and human homologues [191]. Notably, studies have revealed that certain drugs such as ciprofloxacin or levofloxacin activate MRGPRX2 with EC_{50} values 20–35 times lower than its mouse ortholog, MrbprB2. [4] For instance, the studies of sinomenine demon-

strated significant difference of EC_{50} in MRGPRX2- and MrgprB2-transfected HEK293 cells (EC_{50} = 2318 μM and EC_{50} = 1.84–2.77 μM, respectively) [32,37]. Moreover, the EC_{50} values can vary between different cell models (cell lines vs. primary cells) [186]. Additionally, it has been observed that several antagonists, including L733060 and aprepitant, inhibit SP-induced activation of mouse Mrgprb2 but do not inhibit human MRGPRX2 [192]. These findings suggest significant species–specific differences between human MRGPRX2 and mouse MrgprB2, indicating that MrgprB2 mutant mice may not be suitable models for screening drugs intended for human use.

In vitro and in vivo animal studies can also not exactly reflect the function of MRGPRX2 in human tissues, because the key role in potential MRGPRX2-mediated anaphylaxis may also depend on the receptor's biology and the way of drug administration. Due to low affinity of the receptor and thus the relatively high concentration of substance needed to trigger response, the local concentration of the substance may be difficult to achieve. Examples of drugs such as atracurium have been described, whose plasma concentrations after administration are markedly lower than the calculated EC_{50} for MRGPRX2 [186]. MC_{TC}, which is found predominantly in the skin, expresses high levels of MRGPRX2. Therefore, the TCMs administration route plays an equally important role. Notably, over 80% of TCM anaphylactoid reactions occur during parenteral administration [189], and might result from high local TCM concentration after injection and subsequent potent stimulation of skin MCs. Another possibility is that the receptor may be activated or inhibited by the same compound, depending on its concentration. This dose-dependent effect is known in the case of some opioid drugs, such as nalbuphine [193], where the agonistic or inhibitory effect depends on the concentration of the drug, as well as the levels and conformation of the receptor [194,195]. Moreover, the absence of specific biomarkers for MRGPRX2 activation in vivo complicates human studies and impedes progress in this field.

The available studies on the interaction of natural products and herbal medicines with MRGPRX2 are considerably limited; therefore, caution is advised when drawing final conclusions.

5. Conclusions

Research into exogenous ligands for the MRGPRX2 receptor has grown tremendously in recent years. In addition to some typical groups of drugs, these include numerous substances of natural origin that are used in TCM for therapeutic purposes. In our work we have described representative examples of these. They can show both antagonistic and agonistic effects towards MRGPRX2. However, current data are derived from animal studies and cell lines; and more studies using primary human(ized) models are needed.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jox14010024/s1, Table S1: Methodological details of the studies analysed.

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