Natural chromanols and chromenols comprise a family of molecules with enormous structural diversity and biological activities of pharmacological interest. A recently published systematic review described more than 230 structures that are derived from a chromanol or pd chromenol core. For many of these compounds structure-activity relationships have been described with mostly anti-inflammatory as well as anti-carcinogenic activities. To extend the knowledge on the biological activity and the therapeutic potential of these promising class of natural compounds, we here present a report on selected chromanols and chromenols based on the availability of data on signaling pathways involved in inflammation, apoptosis, cell proliferation, and carcinogenesis. The chromanol and chromenol derivatives seem to bind or to interfere with several molecular targets and pathways, including 5-lipoxygenase, nuclear receptors, and the nuclear-factor \( \kappa \)-light-chain-enhancer \( \text{NFkB} \) pathway. Interestingly, available data suggest that the chromanols and chromenols are promiscuously acting molecules that inhibit enzyme activities, bind to cellular receptors, and modulate mitochondrial function as well as gene expression. It is also noteworthy that the molecular modes of actions by which the chromanols and chromenols exert their effects strongly depend on the concentrations of the compounds. Thereby, low- and high-affinity molecular targets can be classified. This review summarizes the available knowledge on the biological activity of selected chromanols and chromenols which may represent interesting lead structures for the development of therapeutic anti-inflammatory and chemopreventive approaches.

Keywords: chromanols, chromenols, inflammation, cancer, molecular targets
INTRODUCTION

Chromanols and chromenols are collective terms for about 230 structures derived from photosynthetic organisms like plants, algae, cyanobacteria, fungi, corals, sponges, and tunicates (Birringer et al., 2018). Both compound classes are formed by a cyclization of substituted 1,4-benzoquinones. While 6-hydroxy-chromanols are derived from a 2-methyl-3,4-dihydro-2H-chromen-6-ol structure, 6-hydroxy-chromenols are derived from 2-methyl-2H-chromen-6-ol (Figure 1). The respective bicyclic core structure is associated to a side-chain with varying chain length and modifications, resulting in a great diversity of chromanol and chromenol derivates (Birringer et al., 2018). In a systematic review, Birringer and coworkers were the first implying the great potential of these structures by providing a comprehensive overview of the structural diversity and chemical transformation of all 230 chromanols and chromenols known at that time together with their natural source. The aim of the comprehensive review was rather the detailed description of the complexity of this group of compounds than an outline of their biological activity. Based on this systematic review, the intention of our review was to more selectively describe the effects of this class of natural products on signaling pathways involved in inflammation, apoptosis, cell proliferation, and carcinogenesis, and the underlying molecular modes of action for selected chromanols and chromenols. Our review therefore represents a useful and relevant addition to the work of Birringer et al., focusing on the evaluation of selected compounds with known biological activity as possible lead structures for putative therapeutic approaches.

Based on the mentioned inclusion criteria, we here focus on tocopherol (TOH) and tocotrienol (T3) structures, sargachromanols, sargachromenols, and sargachromenol, which show structure-activity relationships with mostly anti-inflammatory as well as anti-carcinogenic activities.

Tocopherols and T3s differ in the saturation of the side-chain and form in its entirety the group of vitamin E. Based on the methylolation pattern of the chromanol ring system α-, β-, γ-, and δ- forms of TOHs and T3s can be distinguished. Oxidative modifications of the terminal side-chain increase anti-inflammatory activities. Therefore, hepatic metabolites of vitamin E are supposed to have important physiological activities and will also be included in this review.

Abbreviations: α-T-13′-COOH, α-13′-carboxychromanol; α-T-13′-OH, α-13′- hydroxychromanol; β-T-13′-COOH, garcinoic acid; AC, amplexichromanol; BMDDM, bone marrow-derived macrophages; CEHC, carboxethylhydroxychromanol; JNK, c-Jun N-terminal kinase; CoA, coenzyme A; COX, cyclooxygenases; CYP, cytochrome P450; ERK, extracellular signal-regulated kinase; IC50, intermediate-chain metabolite; IL, interleukin; iNOS, inducible nitric oxide synthase; IkB, nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor; LCM, long-chain metabolite; LPS, lipopolysaccharide; LO, lipoxygenases; MAPKs, mitogen-activated kinases; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP3, NLR family pyrin domain containing 3; NO, nitric oxide; PARP-1, poly-[ADP- ribose]-polymerase 1; PG, prostaglandin; PMA, phorbol-12-myristat-13-acetate; PMN, polymorphonuclear neutrophils; ROS, reactive oxygen species; SCA, sargachromanols; SCE, sargachromenols; SCM, short-chain metabolites; TX, thromboxane; TOH, tocopherol; TNF-α, tumor necrosis factor α; T3, tocotrienol.

Sargachromanols (SCA), sargachromenols (SCE), and amplexichromanols (AC) have a tocotrienol-derived backbone implying similar biological activities. Our review focuses in more detail on the current knowledge about the biological activity as well as on potential regulatory pathways and molecular targets of chromanols and chromenols.

CHROMANOL AND CHROMENOL STRUCTURES

Chromanols

Tocopherols and Tocotrienols

Vitamin E, more precisely RRR-α-tocopherol, has been identified in 1922 as a vital factor for fertility in rats (Evans and Bishop, 1922). Vitamin E does naturally occur in various plant-derived foods, such as oils, nuts, germs, seeds as well as vegetables and, in lower amounts, fruits. Thus, vitamin E represents the most widely distributed and abundant chromanol in nature. The term vitamin E comprises different lipophilic molecules that consist of the chromanol ring structure with a covalently bound phytanyl-side-chain. Depending on the saturation of the C-16′ side-chain, these molecules are classified as TOH, T3s (Figure 2), and vitamin E related structures named tocochromanols and marine-derived TOHs. Tocopherols are characterized by a saturated phytanyl side-chain whereas tocochromanols, marine-derived TOHs and T3 are unsaturated at either the terminal isoprene unit or have three double bonds within the side-chain (Fujisawa et al., 2010; Kruk et al., 2011). Further, the methylation pattern of the chromanol ring determines the classification as α-, β-, γ-, and δ-forms of TOHs and T3s. Although several similar molecules form the group of vitamin E, only α-TOH seems to have vitamin property in animals and humans. For instance, in rats α-TOH preserves fertility, whereas in humans the deficiency disease ataxia with vitamin E deficiency (AVED) is prevented by α-TOH supplementation (Azizi, 2019).

For a long time, the health-promoting effects of vitamin E were only attributed to its antioxidant properties, but more recent studies revealed additional non-antioxidant functions of vitamin E. It is evident that vitamin E modulates gene expression and enzyme activities and also interferes with signaling cascades (Brigelius-Flohé, 2009; Zingg, 2019). Examples for these regulatory effects are the suppression of inflammatory mediators, reactive oxygen species (ROS) and adhesion molecules, the induction of scavenger receptors as well as the activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) (reviewed in Glauert, 2007; Rimbach et al., 2010; Wallert et al., 2014b; Zingg, 2019).

All forms of vitamin E undergo metabolic degradation in the liver. Although the detailed mechanisms remain poorly understood, the principles of the degradation of vitamin E to vitamer-specific physiological metabolites with intact chromanol ring (the nomenclature as α-, β-, γ- and δ-metabolites is used as described for the metabolic precursors in order to distinguish the

Abbreviations: α-T-13′-COOH, α-13′-carboxychromanol; α-T-13′-OH, α-13′-hydroxychromanol; β-T-13′-COOH, garcinoic acid; AC, amplexichromanol; BMDDM, bone marrow-derived macrophages; CEHC, carboxethylhydroxychromanol; JNK, c-Jun N-terminal kinase; CoA, coenzyme A; COX, cyclooxygenases; CYP, cytochrome P450; ERK, extracellular signal-regulated kinase; IC50, intermediate-chain metabolite; IL, interleukin; iNOS, inducible nitric oxide synthase; IkB, nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor; LCM, long-chain metabolite; LPS, lipopolysaccharide; LO, lipoxygenases; MAPKs, mitogen-activated kinases; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP3, NLR family pyrin domain containing 3; NO, nitric oxide; PARP-1, poly-[ADP- ribose]-polymerase 1; PG, prostaglandin; PMA, phorbol-12-myristat-13-acetate; PMN, polymorphonuclear neutrophils; ROS, reactive oxygen species; SCA, sargachromanols; SCE, sargachromenols; SCM, short-chain metabolites; TX, thromboxane; TOH, tocopherol; TNF-α, tumor necrosis factor α; T3, tocotrienol.
different forms of vitamin E metabolites) is widely accepted (Figure 3). Thus, enzymatic modifications are restricted to the side-chain (extensively reviewed in (Kluge et al., 2016; Schmölz et al., 2016)). α-Tocopherol is the main form of vitamin E in the human body due to its higher binding affinity to the α-tocopherol transfer protein (Hosomi et al., 1997). Thus, we will focus on the metabolic conversion of α-TOH in the following. Nevertheless, it should be noted that all forms of vitamin E (TOHs as well as T3s) follow the same metabolic route. However, due to the unsaturated side-chain, the degradation of T3s requires further enzymes such as 2,4 dienoyl-coenzyme A (CoA) reductase and 3,2-enoyl-CoA isomerase, which are also

![FIGURE 1](image1.png) Chromanol (2-methyl-3,4-dihydro-2H-chromen-6-ol) and (B) chromenol (2-methyl-2H-chromen-6-ol) core structure.

![FIGURE 2](image2.png) Core structure of (A) tocopherol and (B) tocotrienol forms.

| –tocopherol | R₁   | R₂   | R₃   |
|-------------|------|------|------|
| α           | -CH₂ | -CH₃ | -CH₃ |
| β           | -CH₂ | -H   | -CH₃ |
| γ           | -H   | -CH₃ | -CH₃ |
| δ           | -H   | -H   | -CH₃ |

| –tocotrienol | R₁   | R₂   | R₃   |
|--------------|------|------|------|
| α            | -CH₃ | -CH₃ | -CH₃ |
| β            | -CH₃ | -H   | -CH₃ |
| γ            | -H   | -CH₃ | -CH₃ |
| δ            | -H   | -H   | -CH₃ |
involved in the metabolism of unsaturated fatty acids (Birringer et al., 2002). The initial step of α-TOH modification via ω-hydroxylation in the endoplasmic reticulum leads to the formation of the long-chain metabolite (LCM) α-13′-hydroxychromanol (α-T-13′-OH). It is supposed that this hydroxylation is catalyzed by cytochrome P450 (CYP)4F2 and CYP3A4 (Parker et al., 2000; Sontag and Parker, 2002). After its transfer from the endoplasmic reticulum to the peroxisome, α-T-13′-OH is converted to α-13′-carboxychromanol (α-T-13′-COOH) via ω-oxidation, likely via a two-step mechanism involving alcohol and aldehyde dehydrogenases. α-T-13′-OH and α-T-13′-COOH have been found in human serum (Wallert et al., 2014a; Ciffolilli et al., 2015; Giusepponi et al., 2017), supporting the idea of a more complex physiologic role of vitamin E with physiological relevance of its metabolites for various processes. In healthy humans α-TOH is the most abundant form of vitamin E, occurring in concentrations of about 20–30 µM in serum (Péter et al., 2015). However, supplementation of α-TOH increases α-TOH serum concentration in humans up to 90 µM (Dieber-Rotheneder...

| α/β/γ/δ -metabolite | R₄ | sidechain length |
|---------------------|----|-----------------|
| -13′-T-OH          | -OH | 13              |
| -13′-T-COOH        | -COOH | 13         |
| -11′-T-COOH        | -COOH | 11         |
| -9′-T-COOH         | -COOH | 9             |
| -7′-T-COOH         | -COOH | 7             |
| -5′-T-COOH         | -COOH | 5             |
| -3′-T-COOH         | -COOH | 3             |

**FIGURE 3 |** Core structure of (A) tocopherol and (B) tocotrienol metabolites. The substitutions R₁ to R₃ are given in Figure 2 (A) and (B).
et al., 1991). Following supplementation, the hepatic metabolism is enhanced to protect the liver from excessive accumulation of α-TOH. Consequently, metabolites of vitamin E are formed and accumulate in turn in human serum. The LCMs α-T-13′-OH and α-T-13′-COOH were found in concentrations of 1–7 nM and 1–10 nM at baseline, respectively, whereas supplementation of α-TOH increased serum concentrations of the LCMs up to 12–32 nM and 3–55 nM, respectively (Wallert et al., 2014a; Cifolilli et al., 2015; Giusepponi et al., 2017). Recent studies showed that the active metabolites of vitamin E exert effects on lipid metabolism, apoptosis, proliferation, and inflammatory processes as well as xenobiotic metabolism (Wallert et al., 2014a; Jang et al., 2016; Podsun et al., 2017; Schmölz et al., 2017). Finally, α-T-13′-COOH is excreted via bile and feces or is further degraded via several rounds of oxidation to the hydrophilic short-chain metabolite α-carboxethylhydroxycromanol (CEHC), which is largely excreted via urine (Zhao et al., 2010; Johnson et al., 2012; Jiang, 2014). Another characteristic of the hepatic degradation of vitamin E is that the metabolites are chemically modified. In particular, the LCMs and the short-chain metabolites (SCMs) have been found as sulfated or glucuronidated conjugates in different biological matrices (Galli et al., 2002; Wallert et al., 2014a). Freiser and Jiang (2009) reported that more than 75% of γ-CEHC in the plasma of γ-T3-supplemented rats occurred in conjugated form. Further, also the LCMs, especially 13′-COOH and 11′-COOH metabolites were found as conjugates. Conjugation (sulfation or glucoronidation) seems to occur in the liver in parallel to the β-oxidation of the side-chain of vitamin E (Freiser and Jiang, 2009).

Beside the mentioned LCMs, intermediate-chain metabolites (ICMs) and SCMs that are formed via hepatic degradation of the different vitamin E forms, and vitamin E is also the precursor of quinones, representing another class of vitamin E-derived metabolites that exhibit antioxidant activity. Vitamin E quinones, in particular α-TOH-derived quinones, are formed as byproducts of α-TOH oxidation during peroxidation reactions in in vitro systems (Liebler et al., 1990; Infante, 1999). In addition, these metabolites can also be synthesized by photosynthetic organisms (Liebler et al., 1990). Although the knowledge on this group of tocopherol-derived metabolites is sparse, α-TOH quinone has been described as an essential enzymatic cofactor for fatty acid desaturase (Liebler et al., 1990).

The natural compound δ-T3-13′-COOH, also known as δ-garcinoic acid or δ-tocotrienolic acid, shares structural similarity with the δ-T-LCM δ-T-13′-COOH, the second LCM originating from the hepatic metabolism of δ-TOH. As described previously, hepatic metabolism of tocotrienols follows that of tocopherols. Consequently, δ-T3-13′-COOH is formed during the degradation of δ-T3. Since the concentration of δ-T3 in human plasma is below 1% compared to α-TOH, the physiological relevance of δ-T3-13′-COOH in humans is likely low. So far, the detection of δ-T3-13′-COOH in human blood is still pending. However, local accumulation of δ-T3-13′-COOH in cells or tissues cannot be excluded. δ-T3-13′-COOH can be obtained in relatively high amounts and purity from the seeds of Garcinia kola E. Heckel (Bartolini et al., 2019; Wallert et al., 2019), a plant that is used in traditional African ethnomedicine (extensively reviewed in Kluge et al., 2016). This compound can be used as precursor for the semi-synthesis of α- and δ-LCMs (including α-T-13′-OH, α-T-13′-COOH, δ-T-13′-OH, and δ-T-13′-COOH) for experimental use in vitro and in mice and is therefore important for vitamin E metabolite research (Maloney and Hecht, 2005; Birringer et al., 2010). Further, δ-T3-13′-COOH also appeared to be a potent anti-inflammatory (Wallert et al., 2019) and anti-proliferative agent (Mazzini et al., 2009) and has been shown to act as an inhibitor of DNA polymerase β (Maloney and Hecht, 2005), indicating that δ-T3-13′-COOH may disturb base excision repair in tumor cells. A recent preprint of Bartolini et al. described δ-T3-13′-COOH as a potent agonist of PXR, which is known to be involved in inflammatory processes (Bartolini et al., 2019).

Sargachromanols

Sargachromanols (SCA) comprise a group of chromanols that occur in the brown algae family Sargassaceae (Figure 4). Their high structural diversity results from various side-chain modifications, leading to their classification from SCA-A to SCA-S. The entirety of sargachromanols has been isolated from Sargassum siliquastrum and has been classified via two-dimensional nuclear magnetic resonance experiments (Jang et al., 2005; Im Lee and Seo, 2011). The extensive analysis revealed detailed structural differences between the sargachromanols. For example SCA-C contains a 9′-hydroxyl group with R-configuration in the side-chain, while SCA-F has a methoxy group at C-9′ and a hydroxyl group with R-configuration at C-10′ (extensively reviewed in Birringer et al., 2018). SCAs have been reported to exhibit various biological activities, including anti-oxidative (Lim et al., 2019) (SCA-G), anti-osteoclastogenic (Yoon et al., 2012b; Yoon et al., 2013) (SCA-G), anti-inflammatory (Yoon et al., 2012a; Lee et al., 2013; Heo et al., 2014) (SCA-G and SCA-D), as well as anti-diabetic (Pak et al., 2015) (SCA-I) ones. To the best of our knowledge, metabolism of sargachromanols in humans or animals has not been investigated.

Amplexichromanols

Amplexichromanols represent a small group of hydroxylated T3 derivatives found in different parts of Garcinia plants. For instance, lipophilic extracts from the bark of Garcinia amplexicaulis were used to isolate γ-AC and δ-AC (Figure 5). The chemical structure of γ-AC and δ-AC are similar to γ-T3 and δ-T3, respectively, but carry two additional hydroxyl groups at C-13′ and C-14′. In an initial in vitro experiment, δ-AC reduced vascular endothelial growth factor induced cell proliferation in low nanomolar concentrations, while γ-AC had no effect. This observation probably indicates distinct efficiencies for the different amplexichromanols (Lavaud et al., 2013). However, further experiments revealed strong anti-oxidative potential for both compounds (Lavaud et al., 2015), but nothing is known about the metabolism, systemic distribution, tissue accumulation, or excretion of amplexichromanols so far.
Chromenols consist of a 2-methyl-2\textsubscript{H}-chromen-6-ol core that is associated with a side-chain with varying chain length and varying chemical modifications, leading to high structural diversity. The multitude of these compounds can be obtained from photosynthetic organisms like plants, algae, cyanobacteria, fungi, corals, sponges, and tunicates (Birringer et al., 2018). As the current knowledge on the biological functions of chromenol structures is sparse, this review will exemplarily focus on the most studied sargachromenols (Figure 6). Similar to their chromanol counterparts, sargachromenols were named after the brown algae species \textit{Sargassum serratifolium}, from which they have been isolated first (Kusumi et al., 1979). Just like sargachromanols, sargachromenols comprise a molecule class of high structural diversity due to different side-chain modifications. In the first systematic review on the field of chromanols and chromenols, Birringer and coworkers described 15 sargachromenols, 13 compounds with marine origin (brown algae) and two with marine and plant origin (Birringer et al., 2018). As an example, \(\delta\)-SCE, a structure consisting of a \(\delta\)-chromenol ring system with an unsaturated side-chain containing a carboxy group at C-15', is widely distributed in algae of the \textit{Sargassaceae} family but can also be obtained from plants like \textit{Iryanthera juruensis}. Another interesting sargachromenol is dehydro-\(\delta\)-T3, or Sargol, which is supposed to serve as a biosynthetic precursor for most of the sargachromenols and is occurring in brown algae (Birringer et al., 2018). Brown algae from the \textit{Sargassaceae} family have been used in traditional Asian medicine as well as in health promoting diets, revealing a variety of biological functions (Kim et al., 2014). For example, ethanolic extracts from the \textit{Sargassaceae} species \textit{Myagropsis myagroides}, an alga that grows at the coast of East Asia, revealed potent anti-inflammatory activity. After HPLC-based separation, sargachromenols...
(mostly δ-SCE) have been identified as the most potent anti-inflammatory compounds within these extracts, based on their inhibitory effect on nitric oxide (NO) production in lipopolysaccharide (LPS)-treated immortalized murine microglial BV-2 cells (Kim et al., 2014). Beside their anti-inflammatory activity, anti-carcinogenic (Hur et al., 2008), anti-photoaging (Kim et al., 2012), and anti-cholinesterase activities (Choi et al., 2007) have been described for SCEs. Further, sargachromenols isolated from Sargassum macrocarpum mediate nerve-growth-factor-driven neuronal growth in pheochromocytoma of rat adrenal medulla derived PC12D cells (Tsang et al., 2005).

**BIOLOGICAL ACTIVITY OF NATURAL CHROMANOLS AND CHROMENOLS**

Based on published data, we have chosen signaling pathways that are central for inflammation, apoptosis, cell proliferation, and carcinogenesis (Figure 7). Respective effects of tocopherol-
derived (T) and tocotrienol-derived (T3) chromanol and chromenol structures on nuclear receptors and target enzymes were screened and are discussed in the following.

**Inflammation**

Inflammation is essential for wound healing as well as defense and clearance of pathogens (Kunnumakkara et al., 2018). However, excessive and persistent inflammation is a driving force for many chronic diseases. In addition to obvious inflammatory diseases such as rheumatoid arthritis, it is well accepted that cancer, Alzheimer’s disease, and metabolic syndrome-related diseases like atherosclerosis, non-alcoholic fat liver disease, and diabetes mellitus type 2 are triggered by chronic low-grade inflammation (Kunnumakkara et al., 2018). As systemic inflammation is a complex process, this review refers only to inflammatory pathways that have been studied for chromanol and/or chromenol structures. Key regulatory factors and mediators of inflammatory processes in this context are receptors that sense proinflammatory stimuli, e.g. the toll-like receptors (TLRs), intracellular signaling molecules, like mitogen-activated protein kinases (MAPKs), and transcription factors, such as NF-κB or nuclear factor erythroid 2-related factor 2 (Nrf2). Further, enzymes that produce pro-inflammatory mediators such as prostaglandins (PGs) and leukotrienes (LTs) play a central role during the coordinated orchestra of the inflammatory process. This includes cyclooxygenases (COX) and lipoxygenases (LO). Other key players of inflammation are cytokines which are secreted by various cells and affect the interaction and communication between the different types of cells involved in inflammation (Aggarwal, 2009; Kunnumakkara et al., 2018). Important pro-inflammatory cytokines are interleukin (IL)-1β, IL-6, and IL-8 as well as tumor necrosis factor-α (TNF-α). Another important signaling molecule in inflammatory processes is nitric oxide (Aggarwal, 2009). In the following, chromanol and chromenol structures regulating the expression of key pro-inflammatory enzymes and the respective formation of signaling molecules are outlined.

**Chromanols**

A detailed overview on the biological activities of chromanols linked to inflammation is provided in Table 1.

**Tocopherols and Tocotrienols**

Data available for TOHs and T3s correlate with their abundance in humans. Therefore, α- and γ-TOH as well as their respective T3 forms were mostly investigated so far. α-Tocopherol is regarded as the only form within the group of vitamin E that has been shown to mediate actual vitamin E function (Azzi, 2019). Further, α-TOH is considered as the most abundant vitamin E form in human nutrition, followed by γ-TOH. Relevance of T3s as anti-inflammatory compounds has just recently come to fore of research and will be presented in the following sections.

**Tocopherols.** For many years, TOHs were solely known for their anti-oxidative capacity. However, Azzi and colleagues discovered additional gene regulatory effects of α-TOH that are independent from its capacity as an antioxidant. α-TOH revealed distinct effects on nitric oxide- and eicosanoid-mediated inflammation. For instance, α-TOH (10 μM) decreased the expression level of inducible nitric oxide synthase (iNOS) in LPS-stimulated murine RAW264.7 macrophages (Jiang et al., 2000). However, others could not confirm the observed alteration of iNOS expression using 5 μM (Wallert et al., 2015), 20 μM (Schmölz et al., 2017), or even 100 μM (Ciffolilli et al., 2015) α-TOH. In line with this, iNOS-mediated formation of nitric oxide remained unchanged in RAW264.7 macrophages by coincubation with α-TOH (Jiang et al., 2000; Ciffolilli et al., 2015; Wallert et al., 2015). In contrast, the formation of PGE2 was blocked by 23 to 100 μM α-TOH in LPS-stimulated RAW264.7 macrophages (Jiang et al., 2000; Yam et al., 2009; Ciffolilli et al., 2015; Wallert et al., 2015), but not in IL-1β-stimulated A549 epithelial cells (Jiang et al., 2008). Unexpectedly, upstream-regulated COX-2 expression and activity remained unchanged in RAW264.7 macrophages at concentrations of 23 to 100 μM α-TOH. Furthermore, cytokine-mediated inflammation was not regulated by α-TOH (Yam et al., 2009), except for an inhibition of IL-1β gene expression in RAW264.7 macrophages using 100 μM (Ciffolilli et al., 2015; Wallert et al., 2015). Beside external stimuli, induction of inflammation, mainly via the TLR4-NF-κB signaling pathway, senescence of cells, and aging are also known triggers of inflammation (Lasry and Ben-Neriah, 2015). Indeed, 24-months-old mice are characterized by an increased inflammatory state compared to younger mice (six months). Application of 500 ppm α-TOH acetate lowered aging-induced increases of nitric oxide and PGE2 plasma levels as well as COX-2 activity compared to 24-months-old mice fed 30 ppm (Beharka et al., 2002). In line with this, supplementation with 800 mg α-TOH/kg/d in elder humans for 30 days lead to significantly lower levels of PGE2 in plasma and peripheral blood mononuclear cells compared to vehicle-treated controls (Meydani et al., 1990).

The second most abundant form of vitamin E, γ-TOH, is more prominent for its anti-inflammatory capacity compared to α-TOH. Release of nitric oxide by LPS-stimulated RAW264.7 cells was significantly inhibited using 10 μM γ-TOH (Jiang et al., 2000). Release of eicosanoids inflammation, more precisely PGE2, in LPS-stimulated RAW264.7 cells and in IL-1β-stimulated A549 cells was inhibited by 10 μM (IC50 7.5 μM) (Jiang et al., 2000) and 25–40 μM (IC50 4–7 μM) (Jiang et al., 2000; Jiang et al., 2008), respectively. However, COX-2 expression (Jiang et al., 2000; Jiang et al., 2008) and activity (Jiang et al., 2000; Jiang et al., 2016) remained unchanged in LPS-stimulated RAW264.7 macrophages, whereas COX-2 activity was inhibited by 50 μM γ-TOH in IL-1β-stimulated A549 epithelial cells (Jiang et al., 2008). Azoxymethane-induced IL-6 production was dampened in BALB/c mice by a γ-TOH-enriched diet (Jiang et al., 2013).

δ-tocopherol (20 μM) significantly decreased LPS-induced expression of iNOS (by 60% at mRNA and by 48% at protein level) and formation of nitric oxide (by 36%) in RAW264.7 macrophages (Schmölz et al., 2017). Jiang et al. reported an inhibition of COX-2 activity, but not COX-2 expression in IL-1β-stimulated A549 cells (Jiang et al., 2008), whereas Jang et al.
| α-TOH | Eicosanoid-mediated | Cytokine-mediated |
|-------|---------------------|------------------|
| iNOS E | NO PrD | RAW264.7 | 5 µM | 20 µM | 10 µM | NO inhibition | (Wallert et al., 2015) | LPS | NO PrD | RAW264.7 | 10 µM | NO inhibition | (Jiang et al., 2000) | LPS | NO PrD | RAW264.7 | 100 µM | NO inhibition | (Ciffolilli et al., 2015) |
| LPS | NO PrD | RAW264.7 | 10 µM | 50 µM | no inhibition | no inhibition | (Schmölz et al., 2017) | LPS | NO PrD | RAW264.7 | 20 µM | 23 µM | no inhibition | (Yang et al., 2009) | LPS | NO PrD | RAW264.7 | 100 µM | 100 µM | no inhibition | (Ciffolilli et al., 2015) |

| β-TOH |
|-------|---------------------|------------------|
| iNOS E | NO PrD | RAW264.7 | 10 µM | 50 µM | no inhibition | no inhibition | (Jiang et al., 2000) | LPS | NO PrD | m_PM | 500 ppm | inhibition | (Beharka et al., 2002) | LPS | NO PrD | RAW264.7 | 100 µM | 100 µM | no inhibition | (Ciffolilli et al., 2015) |

| γ-TOH |
|-------|---------------------|------------------|
| iNOS PE | NO PrD | RAW264.7 | 10 µM | NO inhibition | (Jiang et al., 2000) | LPS | NO PrD | RAW264.7 | 10 µM | NO inhibition | (Jiang et al., 2000) | LPS | NO PrD | RAW264.7 | 100 µM | 100 µM | no inhibition | (Jiang et al., 2000) |
| LPS | NO PrD | RAW264.7 | 10 µM | 50 µM | no inhibition | no inhibition | (Jiang et al., 2000) | LPS | NO PrD | RAW264.7 | 50 µM | 50 µM | no inhibition | (Jiang et al., 2000) | LPS | NO PrD | RAW264.7 | 10 µM | 50 µM | no inhibition | (Jiang et al., 2000) |

(Continued)
| Nitric oxide | Eicosanoid-mediated | Cytokine-mediated |
|-------------|---------------------|------------------|
| inOS        | NO                  | IL-1β            |
| LPS         | INOS E              | NO               | COX-2 | PGE2 | IL-1β |
| RAW264.7    | 20 µM inhibition    |                  | IL-1β |      |       |
|             |                     |                  | COX-2 | A    |       |
|             |                     |                  | 549 cells | 549 cells | PGE2 PrD |
|             |                     |                  | 40 µM | 50 µM | 25 µM |
|             |                     |                  | adi inhibition | inhibition | inhibition |
| S (Schmölz et al., 2017) | (Jiang et al., 2008) | (Jiang et al., 2008) | | | |
| a-T3        | NO PrD              | IL-1β            | COX-2 | PGE2 | IL-1β |
| RAW264.7    | 20 µM inhibition    |                  | IL-1β |      |       |
|             |                     |                  | COX-2 | RAW264.7 | 23.5 µM |
|             |                     |                  | 10 µM | no inhibition | inhibition |
| (Yam et al., 2009) | (Yam et al., 2009) | (Yam et al., 2009) | | | |
| α-T3        | NO PrD              | IL-1β            | COX-2 | PGE2 | IL-1β |
| RAW264.7    | 20 µM inhibition    |                  | IL-1β |      |       |
|             |                     |                  | COX-2 | RAW264.7 | 23.5 µM |
|             |                     |                  | 10 µM | no inhibition | inhibition |
| (Yam et al., 2009) | (Yam et al., 2009) | (Yam et al., 2009) | | | |
| γ-T3        | NO PrD              | IL-1β            | NO PrD | IL-1β | IL-1β |
| RAW264.7    | 24 µM inhibition    |                  | NO PrD |      |       |
|             |                     |                  | COX-2 | RAW264.7 | 23.5 µM |
| (Yam et al., 2009) | (Yam et al., 2009) | (Yam et al., 2009) | | | |
| α-T3-13'-OH | NO PrD              | IL-1β            | NO PrD | IL-1β | IL-1β |
| RAW264.7    | 10 µM inhibition    |                  | NO PrD |      |       |
|             |                     |                  | COX-2 | RAW264.7 | 23.5 µM |
| (Cifolli et al., 2015) | (Cifolli et al., 2015) | (Cifolli et al., 2015) | | | |
| (Continued) |
| Nitric oxide | Eicosanoid-mediated | Cytokine-mediated |
|--------------|---------------------|-------------------|
| Nitric oxide E | COX-2 | PGE\(_2\) | IL-1β | IL-6 | TNF-α |
| LPS | NO | RAW264.7 | 10 µM | 10 µM | inhibition (Schmölz et al., 2017) |
| INOS E | NO PrD | RAW264.7 | 10 µM | 10 µM | inhibition (Schmölz et al., 2017) |
| RAW264.7 | 10 µM | 10 µM | inhibition |
| α-T-13′-COOH | LPS | COX-2 PE | 5 µM | 5 µM | inhibition |
| (Wallert et al., 2015) | RAW264.7 | RAW264.7 | (Wallert et al., 2015) | inhibition |
| 5 µM | 5 µM | inhibition (Wallert et al., 2015) | COX-2 A | 10 µM | inhibition (Wallert et al., 2015) |
| 5 µM | 5 µM | no inhibition (Wallert et al., 2015) | COX-2 A | 10 µM | no inhibition (Wallert et al., 2015) |
| δ-T-13′-OH | LPS | COX-2 PE | 5 µM | 5 µM | inhibition |
| (Schmölz et al., 2017) | RAW264.7 | RAW264.7 | (Schmölz et al., 2017) | inhibition |
| 5 µM | 5 µM | inhibition (Wallert et al., 2015) | COX-2 A | 10 µM | inhibition (Wallert et al., 2015) |
| δ-T-13′-COOH | LPS | COX-2 PE | 5 µM | 5 µM | inhibition |
| (Schmölz et al., 2017) | RAW264.7 | RAW264.7 | (Schmölz et al., 2017) | inhibition |
| 5 µM | 5 µM | inhibition (Wallert et al., 2015) | COX-2 A | 10 µM | inhibition (Wallert et al., 2015) |
| δ-T-9′-COOH | LPS | COX-2 PE | 4 µM | 4 µM | inhibition |
| (Schmölz et al., 2017) | RAW264.7 | RAW264.7 | (Schmölz et al., 2017) | inhibition |
| 5 µM | 5 µM | inhibition (Jiang et al., 2008) | COX-2 A | 10 µM | inhibition (Jiang et al., 2008) |
| α-T-5′-COOH | – | COX-2 PE | 20 µM | 20 µM | no inhibition |
| (Schmölz et al., 2017) | RAW264.7 | RAW264.7 | (Schmölz et al., 2017) | inhibition |
| 6 µM | 6 µM | inhibition (Jiang et al., 2008) | COX-2 A | 10 µM | inhibition (Jiang et al., 2008) |

(Continued)
| Nitric oxide | Eicosanoid-mediated | Cytokine-mediated |
|-------------|---------------------|------------------|
| INOS | NO | COX-2 | PGE₂ | IL-1β | IL-6 | TNF-α |
| α-T-3′-COOH | | | | | | |
| TNF-α | TNF-α NO PrD | | | LPS | LPS | |
| INOS PE | NO PrD | | | | | |
| EOC-20 cells | RAEC cells | 100 µM | 100 µM | inhibition | | |
| (Grammas et al., 2004) | | | | | | |
| TNF-α/LPS NO PrD | EOC-20 cells | 100 µM | | inhibition | | |
| (Grammas et al., 2004) | | | | | | |
| γ-T-3′-COOH | | | | | | |
| TNF-α | LPS NO PrD | IL-1β NO PrD | | | | |
| INOS E | NO PrD | COX-2 A | COX-2 enzyme | | | |
| EOC-20 cells | RAEC-20 cells | 100 µM | 10 µM | inhibition | | |
| (Grammas et al., 2004) | (Jiang et al., 2000) | | | | | |
| TNF-α/LPS NO PrD | EOC-20 cells | 100 µM | | inhibition | | |
| (Grammas et al., 2004) | | | | | | |
| δ-T3-13′-COOH | | | | | | |
| LPS | LPS NO PrD | IL-1β NO PrD | | | | |
| INOS E | NO PrD | COX-2 A | COX-2 enzyme | | | |
| RAW264.7 | RAW264.7 | 5 µM | 5.1 µM | inhibition | | |
| (Wallert et al., 2019) | (Waller et al., 2019) | | | | | |
| TNF-α/LPS NO PrD | RAW264.7 | 5 µM | | inhibition | | |
| (Wallert et al., 2019) | | | | | | |
| SCA D | | | | | | |
| LPS | LPS NO PrD | IL-1β NO PrD | | | | |
| INOS PE | NO PrD | COX-2 PE | COX-2 enzyme | | | |
| RAW264.7 | RAW264.7 | 15 µM | 15 µM | inhibition | | |
| (Heo et al., 2014) | (Heo et al., 2014) | | | | | |
| SCA E | | | | | | |
| LPS | LPS NO PrD | IL-1β NO PrD | | | | |
| INOS PE | NO PrD | COX-2 PE | COX-2 enzyme | | | |
| RAW264.7 | RAW264.7 | 29 µM | 29 µM | inhibition | | |
| (Lee et al., 2013) | (Lee et al., 2013) | | | | | |
| (Continued) | | | | | |
did not observe altered COX-2 activity after δ-TOH treatment using a human recombinant enzyme-based assay (Jang et al., 2016). However, formation of PGE₂ was significantly blocked (IC₅₀ 1–3 µM) (Jiang et al., 2008). The least abundant form of tocopherols, β-TOH has been rarely studied regarding its anti-inflammatory capacity. Studies available so far did not reveal any anti-inflammatory effects of β-TOH (Jiang et al., 2008).

#### Tocotrienols

Recent publications reported a more pronounced anti-inflammatory capacity of T3s compared to TOHs, with γ-T3 and α-T3 showing the strongest effects. α-, δ-, and γ-T3 significantly decreased LPS-mediated formation of nitric oxide (by 11%, 31%, 19%, respectively) and PGE₂ (by 30%, 55%, 20%, respectively) in RAW264.7 macrophages treated with 23.5 µM of the respective compound (Yam et al., 2009) as well as bone marrow-derived macrophages (BMDMs) using 1 µM of γ-T3 (Kim et al., 2018). Expression of COX-2 mRNA was inhibited by α-, δ-, and γ-T3, whereas protein expression remained unchanged (Jiang et al., 2008; Yam et al., 2009; Kim et al., 2018). In addition, cytokine-driven inflammation is also dampened by α-, δ-, and γ-T3, which reduced the release of IL-6 and TNF-α in LPS-stimulated RAW264.7 cells. However, γ-T3 reduced expression of IL-6 and TNF-α mRNA as well as the secretion of IL-6, but not of TNF-α in this cell model (Yam et al., 2009). Furthermore, first reports suggest inhibitory effects of γ-T3 on the NLR family pyrin domain containing 3 (NLRP3) inflammasome. In brief, 1 µM γ-T3 suppressed mRNA expression of pro-IL-1β and -18 as well as respective formation of active IL-1β and -18. This has been observed in LPS/nigericin- as well as LPS/palmitate-stimulated BMDMs and db/db mice fed with a diet containing 0.1% γ-T3 for eight weeks (Kim et al., 2016; Kim et al., 2018).

### Metabolites of Tocopherols and Tocotrienols

We here present a report on selected structures formed during hepatic catabolism of vitamin E, for which data on the biological activity was available. Metabolites formed during physiological hepatic metabolism of vitamin E are highly potent anti-inflammatory compounds with different efficiencies, depending on their methylation pattern (Azzi, 2019) and the number of isoprene units forming the side-chain (Schmölz et al., 2017). Metabolism of non-α-TOH forms of vitamin E is more pronounced, resulting from the lower affinities of these molecules to the α-tocopherol transfer protein. However, α-metabolites revealed significant anti-inflammatory properties. The most widely studied metabolites are the LCMs α-T-13′-OH and -COOH and the short-chain metabolites α- and γ-3′-T-COOH, likely due to their presence in plasma, feces, and urine, respectively, which may account for their physiological relevance (Jiang et al., 2007).

### Long- and Intermediate-Chain Tocopherol-Derived Metabolites

Birringer and coworkers showed the relevance of the terminal oxidative modification of the side-chain for biological activity (Birringer et al., 2018). During the hepatic metabolism of TOHs, T-13′-OH are the first metabolites that are formed; these LCMs show distinct effects that are different from those of their respective metabolic precursor (for details, see Chapter 2.1.1, Tocopherols and Tocotrienols). Both, α- and δ-T-13′-OH significantly decreased mRNA (29–72% and 87%, respectively) and

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**Table 1** | Continued

| Nitric oxide | Eicosanoid-mediated | Cytokine-mediated |
|-------------|---------------------|-------------------|
| **SCA G** | **NO** | **COX-2** | **PGE₂** | **IL-1β** | **IL-6** | **TNF-α** |
| LPS | LPS | LPS | LPS | LPS | LPS | LPS |
| LPS | NO PrD | COX-2 PrD | PGE₂ PrD | IL-1β PrD | IL-6 PrD | TNF-α PrD |
| RAW264.7 | RAW264.7 | RAW264.7 | RAW264.7 | RAW264.7 | RAW264.7 | RAW264.7 |
| 10 µM | 10 µM | 10 µM | 10 µM | 10 µM | 10 µM | 10 µM |
| inhibition | inhibition | inhibition | inhibition | inhibition | inhibition | inhibition |
| (Yoon et al., 2012a) | (Yoon et al., 2012a) | (Yoon et al., 2012a) | (Yoon et al., 2012a) | (Yoon et al., 2012a) | (Yoon et al., 2012a) | (Yoon et al., 2012a) |
| δ-AC | **IL-1β** | **IL-6** | **TNF-α** |
| SCA G | LPS | LPS | LPS |
| LPS | LPS | LPS | LPS |
| IL-1β PrD | IL-6 PrD | TNF-α PrD |
| monocytes | monocytes | monocytes |
| 1 µM | 10 µM | 10 µM |
| inhibition | inhibition | inhibition |
| (Richomme et al., 2017) | (Richomme et al., 2017) | (Richomme et al., 2017) |

The effects of the respective compounds on inflammation have been divided into activities mediated by nitric oxide (NOS, NO), eicosanoids (COX-2, PGE₂), and cytokines (IL-1β, IL-6, TNF-α). The content of each cell of the table is constructed as follows (read from top to bottom): (i) used stimulus; (ii) investigated parameter; (iii) cell type, tissue, mouse, or other models used for investigation; (iv) used concentration of the respective compound; (v) observed effect on the studied parameter; (vi) reference. When no stimulus was used or was required for the studies, the respective row is marked with a dash. The following abbreviations are used: A, activity; A549, human adenocarcinoma alveolar basal epithelial cells; BALB/c mice, albino laboratory-bred strain of the house mouse; Apoe-/- mice, apolipoprotein E deficient mice; BMDM, bone marrow derived macrophages; COX-2, cyclooxygenase 2; EOC-20, epithelial ovarian cancer cells; E, expression; GE, gene expression; HFD, high-fat diet; h, human; iNOS, inducible nitric oxide synthase; IL, interleukin; db/db mice, leptin receptor activity deficient mice; LPS, lipopolysaccharides; m, murine; RAW264.7, macrophages derived from apobec1 mouse leukemia virus-induced tumor; NO, nitric oxide; ppm, parts per million; PM, peritoneal macrophages; PrD, production; PGE₂, prostaglandin E₂; PE, protein expression; RAEC, rat aortic endothelial cells; TNF-α, tumor necrosis factor α. All results obtained from in vivo studies are marked in gray.
protein (40–53% and 53%, respectively) expression of iNOS and the production of nitric oxide (56–69% and 49%, respectively) in LPS-stimulated murine RAW264.7 macrophages at a concentration of 10 µM, thus showing comparable effect sizes independent from the methylation pattern of the chromanol ring system (Cifflollit et al., 2015; Schmölz et al., 2017). Furthermore, α-T-13′-OH significantly decreased expression of COX-2 mRNA and protein (64% and 49%, respectively), IL-1β (64%) and IL-6 (68%) mRNA, and the production of PGE2 (55%) (Cifflollit et al., 2015).

Notably, the length of the side-chain is important for the mediation of anti-inflammatory effects. Accordingly, both α-T-13′-COOH (5 µM) and δ-T-13′-COOH (5 µM) significantly decreased expressions of iNOS and COX-2 mRNAs as well as proteins in murine LPS-stimulated RAW264.7 macrophages (Wallert et al., 2015; Schmölz et al., 2017). Further, δ-T-13′-COOH inhibited the activity of purified recombinant COX-2 enzyme (5 µM [Jiang et al., 2008; Jang et al., 2016]) as well as in human lung adenocarcinoma A549 cells (4 µM, [Jiang et al., 2008]). Interestingly, the activity of recombinant COX-2 enzymes remained unchanged by α-T-13′-COOH (5–10 µM) (Wallert et al., 2015; Pein et al., 2018). LPS-induced production of the respective signaling molecules, nitric oxide and PGE2, was completely blocked in murine macrophages (5 µM), but not in LPS-activated human primary monocytes (10 µM) (Pein et al., 2018). In addition, 5-LO-induced formation of pro-inflammatory leukotrienes was dampened by α-T-13′-COOH in LPS-stimulated monocytes (LTB4), activated human neutrophils, activated human blood, zymosan-induced mouse peritonitis (LTC4), as measured in plasma and exudate, and ovalbumin-induced bronchial hyperreactivity in mice (Pein et al., 2018). Effective concentrations of α-T-13′-COOH, that inhibit 5-LO product formation in vitro, were in a range that was detected for the metabolite in human and mice serum without supplementation (<0.3 µM). Furthermore, expression of pro-IL-1β was down-regulated by 5 µM α-T-13′-COOH, whereas IL-6 and TNF-α remained unchanged (Wallert et al., 2015).

Degradation of the LCMs of different vitamin E forms results in formation of respective ICMs that are further processed to SCMs. These metabolic end-products do not accumulate in plasma or tissues and their physiological relevance is therefore considered as less important. Hence, data on these metabolites are scarce. To date, anti-inflammatory effects, i.e., the inhibition of COX-2 activity (IC50 6 µM), by δ-9′-T-COOH have been reported in human lung adenocarcinoma A549 cells (Jiang et al., 2008).

Long- and Intermediate-Chain Tocotrienol-Derived Metabolites. Within the group of T3-derived metabolites, the LCM δ-T3-13′-COOH (i.e. garcinoic acid) is the most potent anti-inflammatory compound of the ones studied so far. Expression of iNOS (by 97%), COX-2 (by 70%), pro-IL-1β (by 61%), IL-6 (by 70%), and TNF-α (by 25%) mRNA was decreased by 5 µM δ-T3-13′-COOH in LPS-stimulated murine RAW264.7 macrophages. Consequently, protein expression of iNOS (by 83%), COX-2 (by 33%), and the respective formation of NO (by 81%), PGE2 (by 90%) and thromboxane (TX)B2 (by 91%) were dampened in LPS-stimulated murine RAW264.7 macrophages (Wallert et al., 2019). Formation of PGE2 in LPS-stimulated monocytes was inhibited already by 300 nM δ-T3-13′-COOH (Pein et al., 2018). In line with this, δ-T3-13′-COOH also inhibited activity of microsomal PGE2 synthase (by nearly 70%) at a concentration of 10 µM in a cell-free assay using microsomes of IL-1β-stimulated human lung adenocarcinoma A549 cells as an enzyme source (Alsabil et al., 2016; Pein et al., 2018). However, in ApoE−/− mice fed a high fat diet with 1 mg/kg δ-T3-13′-COOH for 8 weeks neither nitric oxide, PGE2, TXB2 nor IL-1β concentrations in plasma were altered compared to the control group (Wallert et al., 2019). However, contrary data exist also for the alteration of prostaglandins following inhibition of COX-2 activity: IC50 9.8 µM (Jiang et al., 2016) and IC50 >10 µM (Pein et al., 2018).

**Short-Chain Tocopherol-Derived Metabolites.** 5′-T-COOH (CMBHC) and 3′-T-COOH (CEHC) are the SCMs. Physiologically formed γ-3′-T-COOH was mainly detected in urine. Supplementation of α-TOH enhances the hepatic metabolism of α-TOH, which in turn increases degradation of α-TOH and excretion of α-5′-T-COOH and α-3′-T-COOH via urine. Both, α-5′-T-COOH (IC50 140 µM) and γ-3′-T-COOH (IC50 450 µM) showed marginal inhibitory effects on human recombinant COX-2 activity (Jiang et al., 2008). However, in IL-1β-stimulated A549 cells, γ-3′-T-COOH (50 µM) exhibited stronger inhibition of COX-2 activity. Formation of PGE2 was also inhibited in IL-1β-stimulated A549 (50 µM), LPS-stimulated RAW264.7 (10 µM), as well as TNF-α-stimulated RAEC (IC50 59 µM) and EOC-20 cells (IC50 66 µM) (Jiang et al., 2000; Grammas et al., 2004). The TNF-α-induced release of nitric oxide was blocked in EOC-20 (IC50 58 µM) and RAEC cells (IC50 56 µM) by α-3′-T-COOH, whereas 100 µM γ-3′-T-COOH inhibited production of nitric oxide in EOC-20 cells by 10% only (Grammas et al., 2004). In contrast, both α-3′-T-COOH and γ-3′-T-COOH decreased production of nitric oxide in LPS-stimulated EOC-20 cells (Grammas et al., 2004). Notably, lower concentrations did not alter production of nitric oxide (Jiang et al., 2000; Grammas et al., 2004).

**Sargachromanolns**
The sargachromanol forms D, E, and G isolated from *Sargassum silikuinarum* also exert anti-inflammatory effects in LPS-stimulated RAW264.7 macrophages in a concentration-dependent manner. Sargachromanol forms D, E, and G inhibited expression of iNOS protein to 30–50% with concentrations of 15, 12.5, and 20 µM, respectively. In contrast, inhibitory effects on the formation of the respective signaling molecule nitric varies compound-dependent between 10 and 90% (Lee et al., 2013), with SCA E being the most effective (Yoon et al., 2012a; Lee et al., 2013; Heo et al., 2014). Within the inflammatory eicosanoid pathway, expression of COX-2 was inhibited by 15% by SCA D and G and up to 90% by SCA E. The IC50 for the formation of COX-2-derived PGE2 was 15 µM (SCA D [Heo et al., 2014]), 12.5 µM (SCA E [Lee et al., 2013]), and 20 µM (SCA G [Yoon et al., 2012a]), respectively. The LPS-induced production of TNF-α, IL-6 and IL-1β was effectively blocked by SCA D (IC50 >60, >20–25, and 40 µM, respectively.
Amplexichromanols
Amplexichromanols can be distinguished as α-, β-, γ-, δ-forms. δ-Amplexichromanols have been shown to inhibit the secretion of TNF-α (IC50 <10 µM) and IL-1β (IC50 10 µM) in LPS-stimulated monocytes (Richomme et al., 2017). To the best of our knowledge, there are no reports on anti-inflammatory effects of the other forms of AC.

Chromenols
Compared to the complex group of structures comprising the chromanol family, chromenol structures are less ubiquitous. Sargachromenol is described here as a representative of the chromenol structures. An ethanolic extract of Myagropsis myagroides inhibited nitric oxide-, eicosanoid-, and cytokine-mediated pathways and the inflammatory response (Table 2), with sargachromenol being the lead compound in the extract (Kim et al., 2014). Further studies using isolated sargachromenol from different sources confirmed the results obtained by Kim et al. For instance, sargachromanol isolated from the marine brown alga Sargassum serratifolium inhibited peroxinitrite anion-mediated albumin nitration with an IC50 of 5 µM (Ali et al., 2017). Furthermore, the COX-2 pathway was inhibited using 50 µM and 100 ppm sargachromenol isolated from Sargassum micracanthum (Yang et al., 2013) and Iryanthera juruensis seeds (Silva et al., 2007), respectively. Here, the effect sizes of 70 and 84% found by Yang et al. and Silva et al., respectively, are comparable with respect to the inhibition of the expression of COX-2 protein. For the respective signaling molecule PGE2 an IC50 value of 30 µM was defined (Yang et al., 2013). In addition, inhibitory effects were observed for the expression of iNOS protein (95%) and the formation of nitric oxide (IC50 82 µM) (Yang et al., 2013).

Carcinogenesis
For the evaluation of anti-carcinogenic effects of chromanol and chromenol structures, key apoptotic pathways, such as cleavage of poly-[ADP-ribose]-polymerase 1 (PARP-1), caspases 3, 7, 8, and 9 as well as anti-proliferative and cytotoxic properties on cancer cell lines and further markers of carcinogenesis marker in mice were evaluated (Figure 7). In addition, large-scaled human trials investigating preventive and therapeutic effects of some tested compounds will be discussed in the following chapter.

Chromanols
A detailed overview on the biological activities of chromanols linked to carcinogenesis is provided in Table 3.

Tocopherols and Tocotrienols
Like the mediation of anti-inflammatory effects, anti-carcinogenic actions were profoundly investigated for α-TOK

### Table 2 | Overview on the biological activities of chromenols linked to inflammation.

| Nitric oxide | Eicosanoid-mediated | Cytokine-mediated |
|--------------|---------------------|-------------------|
| Sargachromenol | NO | COX-2 | PGE2 | IL-1β | IL-6 | TNF-α |
| LPS | LPS | LPS | LPS | LPS | LPS | LPS |
| INOS PE | NO PrD | COX-2 E | PGE2 PrD | IL-1β PrD | IL-6 PrD | TNF-α PrD |
| BV-2 cells | 2.7 µM | 2.7 µM | 2.7 µM | 2.7 µM | 2.7 µM | 2.7 µM |
| inhibition | inhibition | inhibition | inhibition | inhibition | inhibition | inhibition |
| LPS | LPS | LPS | LPS | LPS | LPS | LPS |
| RAW264.7 | RAW264.7 | 50 µM | RAW264.7 | 50 µM | RAW264.7 | RAW264.7 |
| 50 µM | 50 µM | 50 µM | 50 µM | 50 µM | 50 µM | 50 µM |
| inhibition | inhibition | inhibition | inhibition | inhibition | inhibition | inhibition |
| (Yang et al., 2013) | (Yang et al., 2013) | (Yang et al., 2013) | (Yang et al., 2013) | (Yang et al., 2013) | (Yang et al., 2013) | (Yang et al., 2013) |
| Peroxynitrite | peroxynitrite | – | – | – | – | – |
| NO PrD | NO PrD | NO PrD | NO PrD | NO PrD | NO PrD | NO PrD |
| BSA nitrogen | enzyme | enzyme | enzyme | enzyme | enzyme | enzyme |
| 2.5 µM | 100 ppm | 2.5 µM | 100 ppm | 2.5 µM | 100 ppm | 2.5 µM |
| inhibition | inhibition | inhibition | inhibition | inhibition | inhibition | inhibition |
| (Ali et al., 2017) | (Silva et al., 2007) | (Silva et al., 2007) | (Silva et al., 2007) | (Silva et al., 2007) | (Silva et al., 2007) | (Silva et al., 2007) |

The effects of the respective compounds on inflammation have been divided into activities mediated by nitric oxide (NOs), NOs, eicosanoids (COX-2, PGE2), and cytokines (IL-1β, IL-6, TNF-α). The content of each cell of the table is constructed as follows (read from top to bottom): | used stimulus; | investigated parameter; | cell type or other models used for investigation; | used concentration of the respective compound; | observed effect on the studied parameter; | reference. In the publications where no stimulus was used or was required for the studies, the respective row is marked with a dash. The following abbreviations are used: A, activity; BSA, bovine serum albumin; BV-2, brain microglial cells; COX-2, Cyclooxygenase 2; E, expression; INOS, inducible nitric oxide synthase; IL-1β, interleukin 1β; IL-6, interleukin 6; LPS, lipopolysaccharides; m, murine; RAW264.7, macrophages derived from abelson murine leukemia virus-induced tumor; NO, nitric oxide; PrD, production; PGE2, prostaglandin E2; PE, protein expression; TNF-α, tumor necrosis factor α.
### TABLE 3 | Overview on the biological activities of chromanols linked to carcinogenesis.

| Apoptosis/Necrosis mediated | Proliferation | Viability |
|-----------------------------|--------------|-----------|
| PARP-1                      | Casp8        | Casp9     | Casp3 | Casp7 | MDA-MB-435 | MDA-MB-435 | h_cc cells |
| α-TOH                       |              |           |       |       |            |            | 200 µM     |
| PARP-1 CL                   | Casp8 A      |           |       |       |            |            | no inhibition |
| MDA-MB-231                  | Casp3 A      |           |       |       |            |            | no inhibition |
| MCF-7 cells                 | Casp7 CL     |           |       |       |            |            | no inhibition |
| 23 µM                       | no induction |           |       |       |            |            | no inhibition |
| no induction                |              |           |       |       |            |            | no inhibition |
| (Husain et al., 2011)       |              |           |       |       |            |            | (Campbell et al., 2006) |
| PARP-1 CL                   | Casp8 CL     |           |       |       |            |            | no inhibition |
| SW 480 cells                | Casp3 CL     |           |       |       |            |            | no inhibition |
| HT-116                      | no induction |           |       |       |            |            | no inhibition |
| no induction                |              |           |       |       |            |            | (Campbell et al., 2006) |
| (Campbell et al., 2006)     |              |           |       |       |            |            | (Campbell et al., 2006) |
| β-TOH                       |              |           |       |       |            |            | no inhibition |
| PPAR-1 CL                   | Casp8 CL     |           |       |       |            |            | no inhibition |
| MDA-MB-231                  | Casp3 CL     |           |       |       |            |            | no inhibition |
| MCF-7 cells                 | Casp7 CL     |           |       |       |            |            | no inhibition |
| 46.5 µM                     | no induction |           |       |       |            |            | (Campbell et al., 2006) |
| no induction                |              |           |       |       |            |            | (Campbell et al., 2006) |
| γ-TOH                       |              |           |       |       |            |            | no inhibition |
| PPAR-1 CL                   | Casp8 CL     |           |       |       |            |            | no inhibition |
| SW 480 cells                | Casp3 CL     |           |       |       |            |            | no inhibition |
| HCT-116                     | no induction |           |       |       |            |            | no inhibition |
| 25 µM                       |              |           |       |       |            |            | (Azzi et al., 2003) |
| inhibition                  |              |           |       |       |            |            | (Gysin et al., 2002) |
| δ-TOH                       |              |           |       |       |            |            | no inhibition |
| α-T3                         |              |           |       |       |            |            | no inhibition |

(Continued)
### TABLE 3 | Continued

| Apoptosis/Necrosis mediated | Proliferation | Viability |
|-----------------------------|--------------|-----------|
| PARP-1 | Casp8 | Casp9 | Casp3 | Casp7 | MDA-MB-435 | m_B16(F10) | SCID mice |
| PARP-1 CL, MDA-MB-231, MCF-7 cells | Casp8 A | Casp9 A | Casp3 A | Casp7 CL | 211.9 µM | 110 µM | 200 mg/kg |
| 23.5 µM induction (Loganathan et al., 2013) | | | | | MCF-7 cells | inhibition (He et al., 1997) | no reduction (Husain et al., 2011) |
| | MiaPaCa-2 | 50 µM | induction (Husain et al., 2011) | | | | |
| | | | | | | | |
| PARP-1 CL | MiaPaCa-2 | 50 µM | no induction (Husain et al., 2011) | | | | |
| | | | | | | | |
| β-T3 | PARP-1 CL, MDA-MB-231, MCF-7 cells | Casp8 A | Casp9 A | Casp3 A | Casp7 CL | MDA-MB-231 | m_B16(F10) | SCID mice |
| 24.2 µM induction (Loganathan et al., 2013) | | | | | 23.5 µM | | |
| | MiaPaCa-2 | 50 µM | induction (Husain et al., 2011) | | | | |
| | | | | | | | |
| γ-T3 | PARP-1 CL, MDA-MB-231, MCF-7 cells | Casp8 A | Casp9 A | Casp3 A | Casp7 CL | SKBR3, BT474 | rh_RLh-84 | MiaPaCa-2, |
| 20 µM induction (Loganathan et al., 2013) | | | | | PC-3, LNCaP | 50 µM | 50 µM | 50 µM |
| | MiaPaCa-2 | 30/90 µM | induction (Husain et al., 2011) | | | inhibition | reduction (Sakai et al., 2004) | |
| | | 30/90 µM | induction (Yap et al., 2008) | | | | |
| | | | | | | | |
| | PARP-1 CL | MDA-MB-435 | 73.2 µM | MCF-7 cells | 4.9 µM | reduction (Yap et al., 2008) | |
| PC-3, LNCaP | rh_RLh-84 | 25 µM | Induction (Sakai et al., 2004) | | | | |
| 30/90 µM induction (Yap et al., 2008) | | | | | | | |
| | | | | | | | |
| δ-T3 | PARP-1 CL, MDA-MB-231, MCF-7 cells | Casp8 A | Casp9 A | Casp3 A | MDA-MB-435 | m_B16(F10) | SCID mice |
| 25.2 µM induction (Loganathan et al., 2013) | | | | | 226.8 µM | | |
| | MiaPaCa-2 | 50 µM | induction (Husain et al., 2011) | | | MCF-7 cells | inhibition (Yap et al., 2008) | no reduction (Husain et al., 2011) |
| | | | | | | | |
| | PARP-1 CL | MiaPaCa-2 | 50 µM | induction (Husain et al., 2011) | | | | |
| | | | | | | | |

(Continued)
### TABLE 3 | Continued

| Apoptosis/Necrosis mediated | Proliferation | Viability |
|----------------------------|---------------|-----------|
| **PARP-1** Casp8 Casp9 Casp3 Casp7 | | |
| (Husain et al., 2011) | | |
| | | |
| **α-T-13'-OH** (tocopherol derived) | | |
| PARP-1 CL HepG2 cells 20 µM no induction (Birringer et al., 2010) | Casp9 CL HepG2 cells 20 µM no induction (Birringer et al., 2010) | Casp7 CL HepG2 cells 20 µM no induction (Birringer et al., 2010) | m_C6 cells 10 µM reduction (Mazzini et al., 2009) THP-1 ΜΦ 100 µM no reduction (Wallert et al., 2014a) |
| | | | |
| **α-T-13'-COOH** (tocopherol derived) | | |
| PARP-1 CL HepG2 cells 20 µM induction (Birringer et al., 2010) | Casp9 CL HepG2 cells 20 µM induction (Birringer et al., 2010) | Casp7 CL HepG2 cells 20 µM induction (Birringer et al., 2010) | THP-1 ΜΦ 7.4 µM reduction (Wallert et al., 2014a) HepG2 cells 13.5 µM reduction (Birringer et al., 2010) |
| | | | |
| **δ-T-13'-OH** (tocopherol derived) | | |
| PARP-1 CL HepG2 cells 20 µM induction (Birringer et al., 2010) | Casp9 CL HepG2 cells 20 µM induction (Birringer et al., 2010) | Casp7 CL HepG2 cells 20 µM induction (Birringer et al., 2010) | THP-1 100 µM reduction (Schmölz et al., 2017) HepG2 cells 50 µM no reduction (Birringer et al., 2010) |
| | | | |
| **δ-T-13'-COOH** (tocopherol derived) | | |
| PARP-1 CL HepG2 cells 20 µM induction (Birringer et al., 2010) | Casp9 CL HepG2 cells 20 µM induction (Birringer et al., 2010) | Casp7 CL HepG2 cells 20 µM induction (Birringer et al., 2010) | HCT-116 6.5 µM reduction (Jang et al., 2016) HepG2 cells 8.9/8.6 µM reduction (Jang et al., 2016) |
| | | | |
| **α-T-3'-COOH** (tocopherol derived) | | |
| PARP-1 CL HepG2 cells 20 µM induction (Jang et al., 2016) | Casp9 CL HepG2 cells 20 µM induction (Jang et al., 2016) | Casp7 CL HepG2 cells 20 µM induction (Jang et al., 2016) | HCT-116 6.5 µM reduction (Jang et al., 2016) HepG2 cells 8.9/8.6 µM reduction (Jang et al., 2016) |
| | | | |
| **γ-T-3'-COOH** (tocopherol derived) | | |
| | | | |
| **δ-T3-13'-COOH** | | |
| | | |

| | (Continued) |
TABLE 3 | Continued

| Apoptosis/Necrosis mediated | Proliferation | Viability |
|-----------------------------|--------------|-----------|
| PARP-1 | Casp8 | Casp9 | Casp3 | Casp7 | m_C6 cells | HCT-116 |
| HCT-116 | 20 µM | induction | HCT-116 | 10 µM reduction | (Mazzini et al., 2009) | HT-29 |
| (Jang et al., 2016) | (Jang et al., 2016) | (Jang et al., 2016) | (Jang et al., 2016) |
| SCA E | PARP-1 CL | Casp8 CL | Casp9 CL | Casp3 CL | h_HL-60 | 50 µM inhibition |
| h_HL-60 | 25 µM | induction | h_HL-60 | 25 µM induction | (Heo et al., 2011) | h_HL-60 |
| induction | (Heo et al., 2011) | (Heo et al., 2011) | (Heo et al., 2011) |
| α-AC | | | | | HepaRG |
| | | | | | 10 µM |
| | | | | | no reduction |
| | | | | | (Richomme et al., 2017) |

The effects of the respective compounds on carcinogenesis have been divided into apoptosis-mediated (PARP-1, caspases 3, 7, 8, and 9) activities as well as activities affecting proliferation and viability. The content of each cell of the table in the apoptosis section is constructed as follows (read from top to bottom): (i) investigated parameter; (ii) cell type model used for investigation; (iii) used concentration of the respective compound; (iv) observed effect on the studied parameter; (v) reference. The content of each table cell in the proliferation as well as viability section is constructed as follows (read from top to bottom): (i) cell type model used for investigation; (ii) used concentration of the respective compound; (iii) observed effect on the studied parameter; (iv) reference. The following abbreviations are used: A, activity; A549, adenocarcinomic human alveolar basal epithelial cells; BALB/c mice, albino laboratory-bred strain of the house mouse; LNCap, androgen-sensitive human prostate adenocarcinoma cells; Casp, caspase; MCF-7-C3, caspase 3 reconstituted MCF-7 cells; CL, cleavage; cc, colon cancer; MDA-MB-23, epithelial human breast cancer cell line; NB2A, fast-growing mouse neuroblastoma cell line; h, human; MCF-7, human breast cancer cell line established by Michigan Cancer Foundation-7; SKBR3, human breast cancer cell line isolated by the Memorial Sloan-Kettering Cancer Center; BT-474, human breast carcinoma ductal cell line; SaOs-2, human osteosarcoma cell line derived from primary osteosarcoma; SW-480, human cell line established from a lymph node metastasis; HCT-116, human colon cancer cell line; HT-29, human colorectal adenocarcinoma cell line; CaCo-2, human epithelial colorectal adenocarcinoma cells; THP-1, human immortalized monocyte-like cell line; HL-60, human leukemia cell line; HepG2, human liver cancer cell line; MaPac2, human pancreatic cancer cell line; Du-145, human prostate cancer cell line; PC-3, human prostate cancer cell line; B16[10], mouse skin melanoma cells; m, murine; m_C6, murine glial cancer cell line; PARP-1, poly (ADP-Ribose)-polymerase 1; HTB-82, rhabdomyosarcoma cell line; rh_IL12-84, rat hepatoma cell line; HepaRG, terminally differentiated hepatic cells derived from a human hepatic progenitor cell line.

All results obtained from in vivo studies are marked in gray.
IC50 of 180 negative human breast cancer cell line MDA-MB-435 with an amount) and inhibits the proliferation of the estrogen receptor

Despite of the promising results outlined above, it should be noticed that several human trials failed to confirm preventive effects of vitamin E, in particular α-TOH, against cancer. The Alpha-Tocopherol Beta-Carotene (ATBC) Cancer Prevention Study examined whether a daily supplementation of 50 mg α-TOH and/or 20 mg β-carotene could prevent lung cancer in male smokers (Virtamo et al., 2014). However, after five to eight years of supplementation of either α-TOH or β-carotene or the combination of both failed to prevent lung cancer (Virtamo et al., 2014). In addition, other human intervention trails revealed disappointing results, with the Selenium and Vitamin E Cancer Prevention Trial (SELECT) representing a very interesting one. The aim of the SELECT study was to investigate the preventive potential of α-TOH and/or selenium on prostate cancer. In the SELECT trial, healthy men received a daily dose of either 400 IU all-rac-α-tocopheryl acetate or 200 µg selenium or a combination of both for an average of 5.5 years (Lippman et al., 2009). Supplementation with both compounds failed to prevent prostate cancer development. Surprisingly, daily supplementation with all-rac-α-tocopheryl acetate was slightly, but not significantly, associated with an increased overall risk for prostate cancer (Lippman et al., 2009). Next, in the 7 to 12 years follow-up the subjects who had received a daily dose of 400 IU all-rac-α-tocopheryl acetate showed a significantly enhanced risk for prostate cancer (Klein et al., 2011). This result indicates that a dietary supplementation with high doses of this vitamin E derivate could result in an increased risk for cancer.

The T3-rich fraction of palm oil is comprised of all T3 forms (α- [25%], γ- [29%], δ-T3 [14%]) relative to the total vitamin E amount) and inhibits the proliferation of the estrogen receptor-negative human breast cancer cell line MDA-MB-435 with an IC50 of 180 µg/ml (Nesaretnam et al., 1995). Based on that finding, single forms of T3s were tested regarding their effects on proliferation and viability of carcinoma cell lines. The α-, γ-, and δ-forms of T3s were found to mediate cancer type specific effectiveness, with breast cancer cell lines being most affected by the treatment with TOHs. Viability and proliferation of MDA-MB-231 (IC50 22.5 µM), MCF-7 (IC50 14.1–26.1 µM), and MDA-MB-435 cells (IC50: 211.9 µM) were concentration-dependently affected by α-T3 treatment independent on whether they were responsive to estrogen and estradiol (Guthrie et al., 1997; Nesaretnam et al., 1998; Loganathan et al., 2013). However, whereas cleavage of PARP-1 (Loganathan et al., 2013) has been observed, general involvement of apoptosis has not been described yet (Birringer et al., 2003). Although cleavage of PARP-1 as well as caspas 3 and 8 has been observed in pancreatic MiaPaCa-2 carcinoma cells, 50 µM α-T3 had no effect on cell viability (Husain et al., 2011). In contrast, β-T3 (50 µM) reduced the viability of MiaPaCa-2 cells (Husain et al., 2011). In mice, 200 mg/kg α-T3 did not affect tumor growth of AsPC-1 human pancreatic cancer xenografts (Husain et al., 2011), whereas 110 µM α-T3 suppressed proliferation of murine B16(F10) melanoma cells (He et al., 1997).

Within the group of TOHs and T3s, γ-T3 is the most potent anti-carcinogenic form that affects cell growth of breast, prostate, pancreas, and hepatic cancer cells, likely due to a preferred incorporation of γ-T3 in these cells (Sakai et al., 2004). There is strong evidence for the anti-proliferative effects of γ-T3 on breast cancer cell lines MDA-MB-231 (IC50 11.4 µM), MCF-7 (IC50 15.4 µM) (Loganathan et al., 2013), SKBR3 (IC50 4 µM), BT474 (IC50 4 µM) (Alawin et al., 2016), estrogen receptor-negative MDA-MB (IC50 73.2 µM), and estrogen receptor-positive MCF-7 cells (IC50 4.9 µM) (Guthrie et al., 1997).

Metabolites of Tocophersols and Tocotrienols

In contrast to the TOH and T3 forms, the respective metabolites have been rarely investigated regarding their anti-carcinogenic properties. The LCMs of TOHs, namely α-T-13′-COOH (20 µM) and δ-T-13′-COOH (20 µM) induced apoptosis via the mitochondrial pathway, which was shown by cleavage of PARP-1 and caspas 3, 7, and 9, resulting in decreased viability of HepG2 cells (IC50 13.5 µM and 6.5 µM, respectively, Birringer et al., 2010). In human leukemia-derived THP-1 macrophages, viability was decreased by α-T-13′-COOH (IC50 7.4 µM, Wallert et al., 2014a) and δ-T-13′-COOH (IC50 11.1 µM, Schmolz et al., 2017). In addition, δ-T-13′-COOH increased apoptosis-induced cytotoxicity in HCT-116 (IC50 8.9 µM), HT-29 (IC50 8.6 µM) (Jang et al., 2016), and C6 cells (IC50 <10 µM, Mazzini et al., 2009). The T3-derived δ-garcinoic acid decreased the viability of HCT-116, HT-29 (Jang et al., 2016), glioma C6 (Mazzini et al., 2009), and human THP-1 macrophage-like cells (IC50 <20 µM, unpublished data) to a similar extent. In BALB/c mice fed with 0.022%, δ-garcinoic acid in the diet, AOM- and DSS-induced...
colon tumor growth was decreased (Jang et al., 2016). In contrast to the carboxychromanol structures, the hydroxychromanols were less efficient in the cleavage of apoptosis markers and consequently did not affect the viability of HepG2 cells (Birringer et al., 2010) and THP-1 macrophages (Wallert et al., 2014a; Schmölz et al., 2017) at concentrations up to 50 µM and 100 µM, respectively, whereas an anti-proliferative effect on glioma C6 cancer cells was determined using 10 µM α-T-13′-OH (Mazzini et al., 2009). Short-chain metabolites were found to affect growth of prostate cancer cells PC-3 and rhabdomyosarcoma HTB-82 at a concentration of 1 µM (Galli et al., 2004).

**Sargachromanols**

The group of sargachromanols may serve as anti-carcinogenic agents that suppress cell proliferation as reported for SCA E in HL-60 leukemia cells accompanied by cleavage of PARP-1 as well as caspases 3 and 9 (Heo et al., 2011). However, confirmatory data are pending.

**Amplexichromanols**

To date, α-AC has been studied only in HepaRG cells, without effects on viability up to concentrations of 10 µM (Richomme et al., 2017). Therefore, studies on anti-carcinogenic effects of amplexichromanols are still on demand.

**Chromenols**

Within the group of chromenols, δ-sargachromenol is the best-studied one. Previous studies revealed an induction of the cleavage of PARP-1 and caspases along with the induction of apoptosis and reduced cell viability in human skin keratinocyte (HaCaT) cells (Hur et al., 2008). Data obtained from cancer cell lines is still lacking.

INTERFERENCE WITH MOLECULAR TARGETS AND KEY PROTEINS CONNECTING INFLAMMATION AND CARCINOGENESIS

Many signaling molecules involved in inflammatory processes play in parallel also key roles in carcinogenesis. We here exemplarily focus on the interaction of selected chromanols and chromenols with the molecular crosstalk of NF-κB (Jurjus et al., 2016), lipoxigenases (Rädmark et al., 2015; Roos et al., 2016; Merchant et al., 2018), MAPK (Gkouveris and Nikitakis, 2017; Jiménez-Martínez et al., 2019), and the inflammasome (Moossavi et al., 2018; Swanson et al., 2019) due to their accepted involvement in both inflammation and cancer (Figure 7). However, due to the sparse knowledge about their connection to chromanols and chromenols, further topics, like the interaction of tumor and immune cells, adhesion proteins, structure and regulation of tumor microenvironments, mechanisms for programmed cell death as well as other prominent signaling pathways (PI3K/Akt/mTOR; PKC; STAT; Wnt/β-catenin), were not considered in this review.

**Chromanols**

A detailed overview on the interference of chromanols with molecular targets and key enzymes connecting inflammation and carcinogenesis is provided in Table 4.

**Tocopherols and Tocotrienols**

As outlined above, inflammation and carcinogenesis are only marginally affected by α-TOH. This is probably the consequence of a lack of interference of α-TOH with NF-κB. Neither in phorbol-12-myristat-13-acetate (PMA)-stimulated BALBc/3T3 fibroblasts (Azzi et al., 1993), and human pancreatic cancer MiaPaCa-2 cells (Husain et al., 2011), nor TNF-α-stimulated murine myelogenous leukemia KBM-5 cells (Ahn et al., 2007), α-TOH (50 µM), β-TOH (50 µM), or γ-TOH (25 µM) affected NF-κB binding affinity or its activation. In murine RAW264.7 macrophages, 100 µM α-TOH even induced translocation of p65 into the nucleus (Wallert et al., 2015). However, pharmacological doses of α-TOH (500 µM) inhibited NF-κB transcriptional activity as well as the phosphorylation and subsequent degradation of nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor (IkB)-α, the inhibitor of NF-κB, resulting in decreased NF-κB activation in multifactorially stimulated dendritic cells (Tan et al., 2005). γ-Tocotrienol and δ-T3 significantly decreased NF-κB/p65 binding affinity in MiaPaCa-2 cells and diminished p65 subunit translocation in AsPc-1 cells and tumor tissue. In addition, β-T3 and δ-T3 inhibited the translocation in MiaPaCa-2 cells (Husain et al., 2011). The NF-κB inhibitor IkB-α remained unchanged in the aforementioned study. Within the group of T3s, γ-T3 has been described to affect NF-κB activation and p65 subunit translocation in various cell lines and isolated tissue. For example, γ-T3 (20–40 µM) inhibited the phosphorylation of IkB-α and the nuclear translocation of the p65 subunit following various stimuli, including pro-inflammatory cytokines, tumor promoters, carcinogens, and growth factors in different cell lines (Ahn et al., 2007; Yap et al., 2008; Wang et al., 2015). Further, γ-T3 treatment also increased IkB-α protein expression in epididymal adipose tissues isolated from γ-T3-fed db/db mice (Kim et al., 2016) as well as in LPS/palmitate-activated BMDM using 1 µM γ-T3 (Kim et al., 2018). In mice, 400 mg γ-T3/kg, applied orally, sensitized pancreatic tumors to gemcitabine treatment, a drug applied in clinical treatment of pancreatic cancer, by suppressing NF-κB-mediated inflammatory pathways linked to tumorigenesis (Kunnumakkara et al., 2010). The expression of A20 (acronym: TNFAIP3), another inhibitor of NF-κB, was induced by 20 µM γ-T3 in RAW264.7, A549, PC3, and MCF-7 cells (Wang et al., 2015) as well as in peritoneal macrophages obtained from diabetic db/db mice fed with a γ-T3-containing diet (0.1%) (Kim et al., 2016).

5-, 12-, and 15-LO pathways mediate the formation of lipid mediators (including leukotrienes, lipoxins, resolvins, protectins, and maresins), which orchestrate inflammation by triggering immune cell recruitment and allergic responses, and/or actively terminating inflammation, i.e. triggering resolution of inflammation. Leukotrienes and the so-called specialized pro-resolving lipid mediators (produced by the tumor-
TABLE 4 | Overview on the interference of chromanols with molecular targets and key enzymes connecting inflammation and carcinogenesis.

| α-TOH | NF-κB | NLRP3 | MAPKs | Lipoygenases |
|-------|-------|-------|-------|--------------|
| PMA   | LPS   | IL-1β, IL-6, TNF-α | LPS, PGE2, INF-γ | 5-LO A, 5-LO A | AA |
| NF-κB A | NF-κB PE | LPS, PGE2, INF-γ | LPS, PGE2, INF-γ | 5-LO A | 5-LO A | 5-LO PF |
| BALB c/3T3 | Raw264.7 | hDC | hDC | enzyme | enzyme |
| fibroblasts | 50 µM | 100 µM | 500 µM | 500 µM | >1 µM | 1008 µM |
| no inhibition | induction | inhibition | inhibition | inhibition | inhibition | inhibition |
| (Azzi et al., 1993) | (Wallert et al., 2015) | (Tan et al., 2005) | (Tan et al., 2005) |

| β-TOH | PMA | NF-κB A | Balb c/3T3 | no inhibition |
|-------|-----|--------|----------|---------------|
| PMA   | LPS | IL-1β, IL-6, TNF-α | LPS, PGE2, INF-γ | 5-LO A | 5-LO A | 5-LO PF |
| NF-κB A | NF-κB PE | LPS, PGE2, INF-γ | LPS, PGE2, INF-γ | 5-LO A | 5-LO A | 5-LO PF |
| BALB c/3T3 | Raw264.7 | hDC | hDC | enzyme | enzyme |
| fibroblasts | 50 µM | 100 µM | 500 µM | 500 µM | >1 µM | 1008 µM |
| no inhibition | induction | inhibition | inhibition | inhibition | inhibition | inhibition |
| (Azzi et al., 1993) | (Wallert et al., 2015) | (Tan et al., 2005) | (Tan et al., 2005) |

| γ-TOH | TNF-α | NF-κB Actv | KBM-5 | no inhibition |
|-------|-------|-----------|------|---------------|
| PMA   | LPS | IL-1β, IL-6, TNF-α | LPS, PGE2, INF-γ | 5-LO A | 5-LO A | 5-LO PF |
| NF-κB A | NF-κB PE | LPS, PGE2, INF-γ | LPS, PGE2, INF-γ | 5-LO A | 5-LO A | 5-LO PF |
| BALB c/3T3 | Raw264.7 | hDC | hDC | enzyme | enzyme |
| fibroblasts | 50 µM | 100 µM | 500 µM | 500 µM | >1 µM | 1008 µM |
| no inhibition | induction | inhibition | inhibition | inhibition | inhibition | inhibition |
| (Azzi et al., 1993) | (Wallert et al., 2015) | (Tan et al., 2005) | (Tan et al., 2005) |

| δ-TOH | TNF-α Actv | KBM-5 | no inhibition |
|-------|-----------|------|---------------|
| PMA   | LPS | IL-1β, IL-6, TNF-α | LPS, PGE2, INF-γ | 5-LO A | 5-LO A | 5-LO PF |
| NF-κB A | NF-κB PE | LPS, PGE2, INF-γ | LPS, PGE2, INF-γ | 5-LO A | 5-LO A | 5-LO PF |
| BALB c/3T3 | Raw264.7 | hDC | hDC | enzyme | enzyme |
| fibroblasts | 50 µM | 100 µM | 500 µM | 500 µM | >1 µM | 1008 µM |
| no inhibition | induction | inhibition | inhibition | inhibition | inhibition | inhibition |
| (Azzi et al., 1993) | (Wallert et al., 2015) | (Tan et al., 2005) | (Tan et al., 2005) |

(Continued)
### TABLE 4 | Continued

| NF-κB | NLRP3 | MAPKs | Lipoxigenases |
|-------|-------|-------|---------------|
| α-T3  |       |       |               |
| -     | p65 Trl | p65 Trl | AA 5-LO PF |
| -     | MIA PaCa-2 | AsPC-1 | PMNL 85 µM inhibition |
| 50 µM | no inhibition | no inhibition | (Pein et al., 2018) |
|       | (Husain et al., 2011) | (Husain et al., 2011) | |
|       | p65 Trl | m_TT | AA 5-LO enzyme |
|       | MIA PaCa-2 | inhibition | 330 nM inhibition |
|       | (Husain et al., 2011) | no inhibition | (Pein et al., 2018) |
|       | p65 Trl | MIA PaCa-2 | AA 12-LO PF |
|       | (Nucleus) | BA | PMNL 3 µM inhibition |
| 50 µM | no inhibition | no inhibition | (Pein et al., 2018) |
|       | (Husain et al., 2011) | (Husain et al., 2011) | |
|       | p65 Trl | m_TT | AA 15-LO PF |
|       | MIA PaCa-2 | inhibition | 3 µM inhibition |
|       | (Husain et al., 2011) | no inhibition | (Pein et al., 2018) |

| β-T3  |       |       |               |
| -     | p65 Trl | p65 Trl | AA 5-LO A enzyme |
| -     | MIA PaCa-2 | MIA PaCa-2 | AA 12-LO PF |
| 50 µM | no inhibition | no inhibition | PMNL 3 µM inhibition |
|       | (Husain et al., 2011) | (Husain et al., 2011) | (Pein et al., 2018) |

| γ-T3  |       |       |               |
| -     | p65 Trl | p65 Trl | AA 15-LO PF |
| -     | RAW264.7, H1299, A293, MCF-7, 40 µM | U226, SGC4 | PMNL 3 µM inhibition |
| -     | inhibition | 25 µM | (Kim et al., 2016) |
|       | (Yap et al., 2008) | (Ann et al., 2007) | |
| -     | p65 DNA | p65 DNA | AA 5-LO A |
| -     | MIA PaCa-2 | MIA PaCa-2 | AA 5-LO A |
| 50 µM | no inhibition | no inhibition | 95 µM inhibition |
|       | (Husain et al., 2011) | (Husain et al., 2011) | (Pein et al., 2018) |

(Continued)
|       | NF-κB                          | NLRP3                  | MAPKs   | Lipoxigenases |
|-------|--------------------------------|------------------------|---------|---------------|
|       | (Husain et al., 2011)          | (Husain et al., 2011)  | (Wang et al., 2015) | LPS           |
|       | –                              | –                      | –       |               |
| δ-T3  | p65 DNA BA                     | p65 Trl                | p65 Trl | 5-LO A        |
|       | MiaPaCa-2                      | MiaPaCa-1              | MiaPaCa-1,  | 12-LO PF      |
|       | 50 µM                          | 50 µM                  |      | PMNL          |
|       | inhibition                      | inhibition             | inhibition | 3 µM          |
|       | (Husain et al., 2011)          | (Husain et al., 2011)  | (Pein et al., 2018) | no inhibition |
|       | –                              | –                      | –       | (Pein et al., 2018) |
|       | AA                             | AA                     |         |               |
|       | 5-LO A enzyme                  | 170 nM                 | 3 µM    |               |
|       | 5-LO PF                        | 60 µM                  | 3 µM    |               |
|       | 5-LO PF enzyme                 | 350 nM                 | 3 µM    | induction     |
|       | 5-LO PF                        | 190 nM                 | 3 µM    | induction     |
|       | 5-LO PF                        | 270 nM                 | 3 µM    | inhibition    |
|       | 5-LO PF                        | 80 nM                  | 3 µM    | inhibition    |
|       | AA                             | AA                     |         |               |
|       | 5-LO A enzyme                  | 12-LO PF               | 15-LO PF |
|       | 5-LO PF                        | 12-LO PF               | 15-LO PF |
|       | 5-LO PF                        | 15-LO PF               | 15-LO PF |
|       | 5-LO PF enzyme                 | 3 µM                   | 3 µM    | induction     |
|       | 5-LO PF enzyme                 | 3 µM                   | 3 µM    | inhibition    |
|       | 5-LO PF                        | 3 µM                   | 3 µM    | induction     |
|       | 5-LO PF                        | 3 µM                   | 3 µM    | inhibition    |
|       | 5-LO PF                        | 3 µM                   | 3 µM    | induction     |
|       | 5-LO PF                        | 3 µM                   | 3 µM    | inhibition    |
|       | 5-LO PF                        | 3 µM                   | 3 µM    | induction     |
|       | 5-LO PF                        | 3 µM                   | 3 µM    | inhibition    |
|       | 5-LO PF                        | 3 µM                   | 3 µM    | induction     |
|       | 5-LO PF                        | 3 µM                   | 3 µM    | inhibition    |
|       | 5-LO PF                        | 3 µM                   | 3 µM    | induction     |
|       | 5-LO PF                        | 3 µM                   | 3 µM    | inhibition    |
|       | 5-LO PF                        | 3 µM                   | 3 µM    | induction     |
|       | 5-LO PF                        | 3 µM                   | 3 µM    | inhibition    |
|       | 5-LO PF                        | 3 µM                   | 3 µM    | induction     |
|       | 5-LO PF                        | 3 µM                   | 3 µM    | inhibition    |
|       | 5-LO PF                        | 3 µM                   | 3 µM    | induction     |
|       | 5-LO PF                        | 3 µM                   | 3 µM    | inhibition    |
|       | 5-LO PF                        | 3 µM                   | 3 µM    | induction     |
|       | 5-LO PF                        | 3 µM                   | 3 µM    | inhibition    |
|       | 5-LO PF                        | 3 µM                   | 3 µM    | induction     |
|       | 5-LO PF                        | 3 µM                   | 3 µM    | inhibition    |
|       | 5-LO PF                        | 3 µM                   | 3 µM    | induction     |
|       | 5-LO PF                        | 3 µM                   | 3 µM    | inhibition    |
|       | 5-LO PF                        | 3 µM                   | 3 µM    | induction     |
|       | 5-LO PF                        | 3 µM                   | 3 µM    | inhibition    |
|       | 5-LO PF                        | 3 µM                   | 3 µM    | induction     |
|       | 5-LO PF                        | 3 µM                   | 3 µM    | inhibition    |
|       | 5-LO PF                        | 3 µM                   | 3 µM    | induction     |
|       | 5-LO PF                        | 3 µM                   | 3 µM    | inhibition    |
|       | 5-LO PF                        | 3 µM                   | 3 µM    | induction     |
|       | 5-LO PF                        | 3 µM                   | 3 µM    | inhibition    |
|       | 5-LO PF                        | 3 µM                   | 3 µM    | induction     |
|       | 5-LO PF                        | 3 µM                   | 3 µM    | inhibition    |
|       | 5-LO PF                        | 3 µM                   | 3 µM    | induction     |
|       | 5-LO PF                        | 3 µM                   | 3 µM    | inhibition    |
|       | 5-LO PF                        | 3 µM                   | 3 µM    | induction     |
|       | 5-LO PF                        | 3 µM                   | 3 µM    | inhibition    |
|       | 5-LO PF                        | 3 µM                   | 3 µM    | induction     |
|       | 5-LO PF                        | 3 µM                   | 3 µM    | inhibition    |
|       | 5-LO PF                        | 3 µM                   | 3 µM    | induction     |
|       | 5-LO PF                        | 3 µM                   | 3 µM    | inhibition    |
|       | 5-LO PF                        | 3 µM                   | 3 µM    | induction     |
|       | 5-LO PF                        | 3 µM                   | 3 µM    | inhibition    |
| NF-κB | NLRP3 | MAPKs | Lipooxygenases |
|-------|-------|-------|----------------|
|       |       |       | 5-LO PF PMNL  |
|       |       |       | 540 nM inhibition |
|       | AA    |       |                 |
|       |       |       |                 |
| δ-T-13′-COOH |       |       | 5-LO PF PMNL  |
|       |       |       | 540 nM inhibition |
|       | AA    |       |                 |
|       |       |       |                 |
|       | δ-T3-13′-COOH |       | 5-LO PF PMNL  |
|       |       |       | 540 nM inhibition |
|       | AA    |       |                 |
|       |       |       |                 |
|       | α-T-5′-COOH |       | 5-LO PF PMNL  |
|       |       |       | 540 nM inhibition |
|       | AA    |       |                 |
|       |       |       |                 |
| α-T-3′-COOH |       |       | 5-LO PF PMNL  |
|       |       |       | 540 nM inhibition |
|       | AA    |       |                 |
|       |       |       |                 |
| δ-T3-13′-COOH |       |       | 5-LO PF PMNL  |
|       |       |       | 540 nM inhibition |
|       | AA    |       |                 |
|       |       |       |                 |

(Continued)
| SCA D | NF-κB | NLRP3 | MAPKs | Lipoxigenases |
|-------|-------|-------|-------|---------------|
| LPS   | p65 Phos | LPS  | JNK Phos | enzyme |
|       | IκB-α Phos | RAW264.7 | RAW264.7 | 1 µM |
| 60 µM | 60 µM | inhibition | 30 µM | inhibition |
| (Heo et al., 2014) | (Heo et al., 2014) | (Lee et al., 2013) | (Lee et al., 2013) |

| SCA E |
|-------|
| LPS   | IL-1β |
|       | p65/p50 Phos |
| ERK Phos | IL-1β |
| MG-63  | MG-63 |
| 40 µM | 40 µM |
| inhibition | inhibition |
| (Yoon et al., 2012b) | (Yoon et al., 2012b) |

| SCA G |
|-------|
| IL-1β |
| p65/p50 Phos |
| MG-63  |
| 40 µM | enzyme |
| inhibition | 1 µM |
| (Yoon et al., 2012b) | (Yoon et al., 2012b) |

(Continued)
microenvironment, in particular by 15-LO-expressing macrophages of the M2 subtype) have further been shown to play pivotal roles in tumor initiation and development as well as angiogenesis and metastasis (Serhan, 2014; Rådmark et al., 2015; Wculek and Malanchi, 2015; Gilligan et al., 2019). All forms of TOHs inhibit the activity of the isolated 5-LO enzyme in the following sequence of their inhibitory capacity: \( \delta \)-TOH (IC\(_{50}\) 0.31 \( \mu \)M) < \( \beta \)-TOH (IC\(_{50}\) 0.75 \( \mu \)M) < \( \alpha \)-TOH (IC\(_{50}\) 1–5 \( \mu \)M) = \( \gamma \)-TOH (IC\(_{50}\) 0.9–3 \( \mu \)M) (Reddanna et al., 1985; Pein et al., 2018). In activated polymorphonuclear leukocytes (PMNL), inhibitory concentrations are 10- to 100-fold higher with the following order: \( \beta \)-TOH < \( \delta \)-TOH < \( \gamma \)-TOH < \( \alpha \)-TOH (Pein et al., 2018). However, activity of 12- and 15-LO, which catalyze the \( 5\)-LO activity with an IC\(_{50}\) value of 80 nM followed by \( \delta \)-TOH (IC\(_{50}\) 0.9–3 \( \mu \)M) (Reddanna et al., 1985; Pein et al., 2018). Notably, in BMDMs treated with chloroquine, an inhibitor of lysosomal degradation, the accumulation of microtubule-associated protein 1A/1B-light chain 3 (LC3)-II, and the degradation of p62 were decreased implying that \( \gamma \)-T3 co-regulates autophagosome formation and inflammasome activation (Kim et al., 2016).

**Metabolites of Tocopherols and Tocotrienols**

Tocopherols and T3s inhibit the activity of isolated recombinant human 5-LO enzyme 10- to 100-fold more efficiently than in activated PMNL. The respective long-chain TOH- and T3-derived metabolites inhibited isolated 5-LO to a similar extent (Jiang et al., 2011; Jiang et al., 2016; Pein et al., 2018). Notably, in activated PMNL, \( \alpha \)-T-13′-COOH was the most potent inhibitor of 5-LO activity with an IC\(_{50}\) value of 80 nM followed by \( \alpha \)-T-13′-OH (190 nM), \( \delta \)-T-13′-OH (540 nM), and \( \delta \)-T-13′-COOH (2 \( \mu \)M) (Pein et al., 2018). Treatment of activated PMNL with 3 \( \mu \)M LCM effectively blocked 12- and 15-LO product formation, whereas only the 12-LO pathway was blocked by \( \alpha \)-T-3′-COOH, \( \alpha \)-3′-T-COOH, and \( \gamma \)-3′-T-COOH (Pein et al., 2018). Conversion of arachidonic acid to leukotrienes via 5-LO was blocked by \( \delta \)-T-3′-13′-COOH (human recombinant enzyme: IC\(_{50}\) 35–57 nM) (Richomme et al., 2017; Pein et al., 2018) and 1 \( \mu \)M (Jang et al., 2016; neutrophils IC 260–345 nM) (Richomme et al., 2017; Pein et al., 2018), whereas product formation

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**TABLE 4 | Continued**

| NF-\( \kappa \)B | NLRP3 | MAPKs | Lipoxigenases |
| --- | --- | --- | --- |
| 40 \( \mu \)M inhibition (Yoon et al., 2012) |
| (Kaminska, 2005). Inhibitory effects of \( \gamma \)-T3 on the MAPK pathway, more precisely the phosphorylation of ERK, p38 and JNK have been observed in epididymal adipose tissues from \( \gamma \)-T3-fed \( db/db \) mice (0.1% of the diet), in LPS-activated BMDMs using 0.5 \( \mu \)M \( \gamma \)-T3 (Kim et al., 2016), and in TNF-\( \alpha \)-activated RAW266.7 cells (Wang et al., 2015). The relevance of NLRP3 inflammasome activation and subsequent formation of pro-inflammmatory cytokines, namely IL-1\( \beta \) and IL-8, in inflammation and related diseases has been shown. \( \gamma \)-T3 decreased NLRP3 inflammasome activation by inhibiting the mRNA and protein expression of the NLRP3 inflammasome in BMDM activated with LPS/palmitate, rather than with LPS/ nigericin, in peritoneal macrophages and adipose tissue isolated from \( \gamma \)-T3-fed \( db/db \) mice (Kim et al., 2016). In addition, in BMDMs treated with chloroquine, an inhibitor of lysosomal degradation, the accumulation of microtubule-associated protein 1A/1B-light chain 3 (LC3)-II, and the degradation of p62 were decreased implying that \( \gamma \)-T3 co-regulates autophagosome formation and inflammasome activation (Kim et al., 2016).
TABLE 5 | Overview on the interference of chromenols with molecular targets and key enzymes connecting inflammation and carcinogenesis.

| NF-κB | MAPKs |
|-------|-------|
| Sargachromenol | |
| TNF-α | TNF-α | LPS | TNF-α | LPS | LPS |
| p65 Trl | p65 PE | LPS | p65 Trl | iκB-α Phos | LPS |
| HUVEC | HUVEC | LPS | BV-2 | HUVEC | BV-2 |
| 40 µM | 60 µM | LPS | 60 µM | 60 µM | 60 µM |
| inhibition | inhibition | LPS | inhibition | inhibition | no inhibition |
| (Gwon et al., 2017) | (Gwon et al., 2017) | (Kim et al., 2014) | (Kim et al., 2014) | (Kim et al., 2014) |
| TNF-α | LPS | LPS | LPS | LPS |
| IκB-α Phos | LPS | LPS |
| HUVEC | BV-2 |
| 40 µM | 60 µM |
| inhibition | inhibition |
| (Gwon et al., 2017) | (Kim et al., 2014) |

The content of each cell of the table is constructed as follows (read from top to bottom): (i) used stimulus; (ii) investigated parameter; (iii) cell type, tissue, mouse, or other models used for the studies; (iv) used concentration of the respective compound; (v) observed effect on the studied parameter; (vi) reference. The following abbreviations are used: BV-2, brain microglial cells transformed by recombinant retrovirus (v-raf/v-mic); JNK, c-Jun N-terminal kinase; ERK, extracellular-signal regulated kinase; HUVEC, human umbilical vein endothelial cells; LPS, lipopolysaccharide; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; p65, nuclear factor NF-κB p65 subunit; IκB, nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor; Phos, phosphorylation; PE, protein expression; Trl, translocation; TNF-α, tumor necrosis factor α.

FIGURE 8 | Heatmap illustrating the effectiveness of chromanol and chromenol structures on selected targets. If not indicated otherwise, the plotted effects represent inhibitory effects of the respective compound on distinct parameters; induced parameters are marked with an arrow (↑). The color coding of the presented heat map ranges from high-affinity targets and parameters (effect with <1 µM) presented in red to low-affinity targets and parameters (effects with >1 µM to ≤100 µM) presented in dark blue. If a compound did not affect a specific factor/parameter or showed low effectiveness (>100 µM), the factor/parameter is marked in light gray. Factors and parameters lacking data are marked in white. The heat map is considered as simplified guide for orientation and does not provide a detailed summary of the topic. All concentrations are given micromole (µM). Abbreviations used are: Actv, activation; A, activity; BA, binding affinity; C, cleavage; E, expression; PF, product formation; P, production; T, translocation.
mediated by 12- and 15-LO remained unchanged (Jang et al., 2016). The discrepancy in IC50 values in the inhibition of cell-free 5-LO likely depends on the different assay conditions. While Pein et al. analyzed specific 5-LO products by reverse-phase high-performance liquid chromatography with ultraviolet detection, Jang et al. used an indirect colorimetric assay, which determines the formation of hydroperoxides. For SCMs, namely 5′-T-COOH and 3′-T-COOH, no inhibitory effect was observed at the tested concentrations up to 3 µM, except for α-5′-T-COOH (IC50 750 nM) (Pein et al., 2018).

Sargachromanols
Blocking of NF-κB activation with SCAs by inhibiting the phosphorylation of p65 and 1xB-α, thereby protecting 1xB-α from degradation, has been shown in LPS-activated RAW264.7 macrophages (Heo et al., 2014) and in IL-1β-activated MG-63 osteosarcoma fibroblasts (Yoon et al., 2012b) for SCA D (60 µM) and G (20 µM), respectively. In addition, interference of SCAs D, E, and G with the MAPK pathways, namely phosphorylation of JNK, ERK, and p38, has been observed in LPS-stimulated RAW264.7 macrophages and IL-1β-activated MG-63 osteosarcoma fibroblasts (Yoon et al., 2012b; Lee et al., 2013; Heo et al., 2014).

Chromenols
Like SCAs, δ-SCE has been shown to interfere with the NF-κB and the MAPK pathways. In TNF-α-stimulated endothelial cells (Gwon et al., 2017) and LPS-stimulated microglia cells (Kim et al., 2018), p65 translocation and the phosphorylation of 1xB-α were inhibited by 40 µM and 60 µM δ-SCE, respectively. In the same cell models inflammation-induced phosphorylation of JNK and ERK was diminished by δ-SCE, whereas p38 remained unchanged (Kim et al., 2018) (Table 5).

LOW AND HIGH-AFFINITY MOLECULAR TARGETS

The heat map in Figure 8 provides a simplified overview about high- and low-dose bioactivities of the different chromanols and chromenols for a rapid assessment. The selection of compounds and parameters is based on a comprehensive review of the current literature about chromanols and chromenols and focusses on the important biological functions described for these compounds in the context of inflammation and cancer. For reasons of simplification, we did not take into account compound-specific uptake kinetics or cell type- or animal model-specific differences. For more detailed information, the reader is referred to Tables 1–5 which summarize our current knowledge on the chromanols and chromenols described in the respective sections. For comparison, presented concentrations are IC50 values or the lowest reported concentrations affecting the respective parameters.

In the studies considered here, T3s often showed higher effectiveness on the induction or suppression of biological activities linked to inflammation and cancer than TOHs. Furthermore, oxidative modification of the terminal side-chain often substantially increases the anti-inflammatory capacity of respective compounds compared to parental compounds, such as TOHs and T3s. Amplexichromanols, sargachromanols and sargachromanols are also characterized by oxidative modifications of the side-chain, which might rationalize potent interactions with inflammatory targets, which needs further investigation. Notably, regulation of different target genes, proteins, and nuclear receptors can hardly be generalized. For instance, within the group of investigated targets, 5-LO is mostly inhibited by a few compounds, with δ-T3-13′-COOH showing strongest inhibitory effects (IC50 35 nM) and α-TOH showing the least (IC50 1 µM). In contrast, the COX-2-regulated formation of signaling molecules is most efficiently inhibited by γ-T3. In summary, especially 5-LO seems to represent a high affinity (affected at concentrations <1 µM) and therefore specific target for the LCMs of vitamin E. Most of the other observed effects, like mediation of caspase activity, anti-proliferative effects, inhibition of NO formation, are probably the result of a stimulation involving low-affinity targets (affected at concentrations ≥ 1 µM). However, as implied by the heat map in Figure 8, further studies are required for a comprehensive evaluation of the potential of chromanol and chromenol structures to serve as lead structures for the development of future anti-inflammatory therapeutic approaches.

CONCLUSION

For our review, we selected chromanols and chromenols for which data on anti-inflammatory and anti-carcinogenic effects were available in public databases of the scientific literature. The structures of our interests were tocopherols, tocotrienols, and their respective metabolites (which are produced in the liver under physiological and pathophysiological conditions) as well as structurally related compounds including sargachromanols, sargachromanols, and amplexichromanols. Criteria for the evaluation of compounds as possible lead structures for future therapeutic targets were their effects on key inflammatory and apoptotic pathways, proliferation, and interaction with (nuclear) receptor and enzymes that connect inflammation with carcinogenesis. Within this group of selected structures, tocopherols, more precisely α-TOH, are by far the most extensively studied compounds. However, the effects of TOHs are mostly only marginal compared to other compounds described in this review.

It should be noted that the methylation pattern of the chromanol ring system significantly affects inflammation and carcinogenesis. For instance, non-α-TOH and non-α-T3 forms affect eicosanoid- and cytokine-mediated inflammation as well as the cleavage of caspases that mediate apoptosis. Further, T3s are more potent in inhibiting caspase cleavage compared to the respective TOH forms. Tocopherol- and T3-derived metabolites and carboxychromanols more than hydroxychromanols inhibit LO, and in particular 5-LO, effectively and reduce the viability of multiple cancer cell lines. Furthermore, sargachromanols interact...
with MAPK and NF-κB pathways, assuming their crosstalk with both, carcinogenesis and inflammation, while sargachromenols mediate anti-carcinogenic effects. Although our knowledge about biological activities of amplexichromanols is sparse, first results indicate their potential for pharmacological applications.

The development of clinically relevant nitric oxide-, eicosanoid-, or cytokine-inhibiting agents or agents that interact with signaling pathways of inflammation is challenging with respect to selectivity and toxicity. Next, although blocking in inflammation is meant to be protective, its permanent or long-term inhibition may cause damage to the body (Brasky et al., 2017). Although detrimental effects of naturally occurring chromanols and chromenols cannot be excluded yet, they are less likely for this group of lead compounds in light of the good tolerability of TOHs and T3s at low to moderate doses. Further studies are required to evaluate whether the observed effects of chromanols and chromenols on inflammation and carcinogenesis are indeed beneficial in humans. Until today, no human clinical trials have been published that provide valid information on the biological activity, bioavailability, kinetics, systemic distribution, or local accumulation of these compounds. However, this groups of molecules appears to be promising as lead structures for future anti-inflammatory and/or anti-cancerogenic therapeutic approaches.

LIMITATIONS

Our review is based on a recent systematic review of Birringer et al. (2018), which presented the first comprehensive overview on the diversity of chromanol and chromenol structures and their biological functions. The aim of our review was to more selectively describe the effects on signaling pathways involved in inflammation, apoptosis, cell proliferation, and carcinogenesis and the underlying modes of action for selected chromanols and chromenols. We are aware of the lack of data for a variety of chromanol structures in our overview. We therefore focused on chromanols and chromenols only where adequate data was available that reported anti-inflammatory and anti-carcinogenic properties. For a more detailed description of the structural and chemical properties of all 230 chromanol and chromenol structures, the reader is referred to (Birringer et al., 2018).

AUTHOR CONTRIBUTIONS

MW and SK wrote the manuscript. MW, SK, MS, MB, and SL designed and structured the manuscript, MS, MB, SL, AK, and OW supervised the project and carefully read, evaluated, and discussed the content of the manuscript.

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