Original Article

Rosa canina – Rose hip pharmacological ingredients and molecular mechanics counteracting osteoarthritis – A systematic review

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ABSTRACT

Background: The successful use of rose hip for the treatment of osteoarthritis is well documented. Several randomized placebo controlled double-blind studies, as mono or combination therapy, have demonstrated treatment efficacy as well as excellent tolerability.

Purpose: This review focuses on the molecular mechanism underlying the clinical effects of rose hip in osteoarthritis (OA).

Methods: The database Medline was screened – using the search term “Rosa canina” or “rose hip” – for publications on pharmacological or mechanistic studies with relevance to OA; in addition for findings on pharmacologically active constituents as well as clinical studies. The screening results were complemented by following-up on cited literature.

Results: In particular, 24 pharmacological studies on Rosa canina or preparations thereof were considered relevant. Potent antioxidant radical scavenging effects are well documented for numerous rose hip constituents besides Vitamin C. Furthermore, anti-inflammatory activities include the reduction of pro-inflammatory cytokines and chemokines, reduction of NF-kB signaling, inhibition of pro-inflammatory enzymes, including COX1/2, 5-LOX and iNOS, reduction of C-reactive protein levels, reduction of chemotaxis and chemoluminescence of PMNs, and an inhibition of pro-inflammatory metalloproteases.

Conclusion: The antioxidant and anti-inflammatory effects of Rosa canina match its clinical action – especially considering new findings on the pharmacological disease pattern of OA. The entirety of several compounds including phenolics, terpenoids, galactolipids, carotenoids, fruit acids and fatty oils can be considered responsible for the observed pharmacological and clinical effects. Further research is needed to elucidate how and in which manner single rose hip compounds interact with their molecular pharmacological targets.

Introduction – Osteoarthritis and inflammation

Osteoarthritis (OA) is the most prevalent joint disorder worldwide (Bortoluzzi et al., 2018; Felson et al., 2000; Wirth et al., 2005). The main risk factor is old age: among adults 60 years of age or older approximately 10% of men and 13% of women suffer from symptomatic knee OA (Zhang and Jordan, 2010). The degenerative destruction of articular cartilage and other parts of the joint, as well as secondary bone lesions, lead to a strong negative impact on the quality of life due to joint pain and joint stiffness, which in turn impairs joint function (Herold, 2007; O’Neil and Felson, 2018). At the same time OA accounts for a tremendous socioeconomic burden (Hunter et al., 2014).

Whereas rheumatoid arthritis (RA) is a chronic, systemic, joint-invasive, autoimmune inflammatory disease (Sung et al., 2019), OA was for a long time considered a primarily non-inflammatory joint disorder - mainly caused by imbalanced wear and tear. However, recent immunological evidence demonstrated inflammatory characteristics that clinically emerge as synovitis. Thus histologically, OA may sometimes be indistinguishable from rheumatoid synovial infiltration, with adaptive immunological mechanisms that drive inflammation and tissue destruction (Geyer and Schonfeld, 2018). Since clinically, only few findings may point to RA or OA in such ambiguous cases, the diagnosis

Abbreviations: COX, Cyclooxygenase; CRP, C-reactive protein; GOPO/GLGPG, Galactolipid: (2S)-1,2-di-O-[(9Z,12Z,15Z)-octadeca-9,12,15-trienoyl]-3-O-beta-D-galactopyranosyl glycerol; IL, Interleukin; LDL, Low-density-lipoprotein; MMP, Matrix metalloproteinase; iNOS, inducible nitric oxide synthase; OA, Osteoarthritis; PMNs, Polymorphonuclear leucocytes (peripheral blood neutrophils/leukocytes), derived from the peripheral blood; RA, Rheumatoid arthritis; RONS, Reactive oxygen and nitrogen species; TNF, Tumor necrosis factor-alpha; WOMAC, Western Ontario and McMaster Universities Arthritis Index

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of inflammatory arthropathies should also take osteoarthritis into consideration (DiCarlo and Kahn, 2011; Helbig et al., 1988).

Fig. 1 gives a schematic overview of processes promoting OA, as well as the beneficial actions of *Rosa canina* constituents. On a molecular level, OA is accompanied by inflammatory processes including the overproduction of reactive oxygen and nitrogen species (RONS) (Lepetsos et al., 2018; Portal-Nunez et al., 2016). RONS produced by chondrocytes – and involved in OA – include superoxide, hydrogen peroxide, nitric oxide, and peroxynitrite (Bolduc et al., 2018).

Although RONS are indispensable as second messengers in the regulation of normal physiological processes (and as necessary destructive agents in the immune system’s fight against pathogens), their overproduction by abnormal chondrocyte metabolism exceeds the physiological buffering capacity and results in oxidative stress (Li et al., 2012). The excessive production of RONS can damage proteins, lipids, nucleic acids, and extracellular matrix components (Li et al., 2012). At the same time, both RONS signaling and the induced cellular damage amplify the inflammatory response (Sutipornpalangkul et al., 2009). This includes NF-κB PI3K/Akt and ERK signaling, and expression of inflammatory cytokines (interleukins IL-1β and IL-6) and transcription factors, as well as matrix-degrading enzymes (e.g. the metalloproteinases MMP-3 and MMP-13). This process goes along with chondrocyte senescence (“senescence-associated secretory phenotype”) and permanent cell cycle exit (Lepetsos et al., 2018; Loeser et al., 2016; Portal-Nunez et al., 2016).

RONS are mainly produced by the mitochondrial respiratory chain. For their own protection, mitochondria are enriched with antioxidant defenses - within a healthy cell, the degradation of RONS formed by nutrient oxidation and respiration (or entering the mitochondria from the outside) leads to a RONS homeostasis (Mailloux, 2018). Only healthy mitochondria are able to preserve their RONS homeostasis. Thus, protecting mitochondrial function should be a key therapeutic target in preventing or limiting OA pathogenesis (Wu et al., 2014).

Reduced activity of mitochondrial superoxide dismutase (disabling superoxide) was observed in OA patients. The continuous and with age accumulating oxidative stress can be considered one of the major pathogenetic mechanisms in OA (Aigner et al., 2006; Ruiz-Romero et al., 2009; Scott et al., 2010). In healthy tissue, autophagy removes damaged organelles (Portal-Nunez et al., 2016). However, with age, autophagy levels decline – also due to dysfunction in energy metabolism (reduced activity of 5′-AMP-activated protein kinase) – making mitochondria more susceptible to RONS imbalance with all its consequences (Loeser et al., 2016).

Next to an aging-related increased mitochondrial dysfunction, other aging-related changes favouring OA are age-related inflammation “inflammaging” (RONS are also produced by phagocytic cells during inflammation), cellular senescence and age-related changes in the extracellular matrix.

One of the main life-style related risk factors of OA is obesity. Interestingly, obesity also leads to OA in non-weight-bearing joints. This can be explained by the inflammation-inducing properties of adipose tissue. Adipokines, including adiponectin and leptin regulate inflammatory immune responses in cartilage. The pro-inflammatory cytokines serum tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β) and IL-6 – produced by macrophages derived from adipose tissue – not only promote lipolysis, inhibit lipid synthesis and decrease blood lipids as a negative feedback mechanism, but additionally induce the production of other cytokines, matrix metalloproteinases (MMPs) and prostaglandins and inhibit the synthesis of proteoglycans and type II collagen. In this manner these pro-inflammatory cytokines induce...
cartilage matrix degradation and bone resorption (Wang and He, 2018).

An additional risk factor of OA is a raised serum LDL (Low-density lipoprotein)-cholesterol level (Thomas et al., 2018). Hypercholesterolaemia in turn promotes inflammatory responses, including the induction of Toll-like receptor signaling, inflammasome activation, and the increased production of monocytes and neutrophils from bone marrow and spleen. This again worsens diseases that are associated with chronic metabolic inflammation, including atherosclerosis and obesity (Tall and Yvan-Charvet, 2015). An additional genetic predisposition for OA, as well as an epigenetic regulation has become evident (Barter et al., 2012; Raman et al., 2018; Snochowska et al., 2017). In this context, microRNAs have been shown to regulate gene expression of OA-relevant genes (Malemud, 2018). Metabolites in the synovial fluid and blood correlate with OA incidence and prognosis (Rockel and Kapoor, 2018), which may be used as diagnostic tool in the future.

Methods

In order to reduce bias, the following search criteria were applied:

The literature database Medline was searched using the search term “Rosa canina” or “rose hip” (234 hits as of May 3, 2019). Relevant literature was found by screening for publications on pharmacological or mechanistic studies with relevance to OA (e.g. studies examining anti-inflammatory activity). Furthermore, clinical OA studies and/or reviews on Rosa canina and publications on Rosa canina pharmacologically active constituents were also considered relevant and were used to write the corresponding sections.

Review articles e.g. (Ayati et al., 2018; Cheng et al., 2016) and as well as research articles were used complement the performed literature search by following-up all citations that were relevant to the above search criteria; any additional relevant literature was added.

*Rosa canina* for the treatment of osteoarthritis – clinical evidence

Rose hip is a well-known herbal antiphlogistic which has been used in folk medicine for thousands of years due to its anti-inflammatory and pain-relieving properties (Engels and Brinckmann, 2016). In addition, the efficacy and safety of rose hip for the treatment of osteoarthritis has been studied in several clinical studies.

In a 4-month double-blind placebo-controlled randomized study with 100 OA patients, 5 g rose hip powder/day lead to a significant decrease in joint pain and a significant improvement of joint mobility – both compared to placebo. 64.6% of patients in the rose hip group reported at least some reduction of pain, compared to 43.8% of the placebo-treated patients (Warholm et al., 2003). A double-blind placebo-controlled cross-over study with 112 patients showed a 3-month response rate regarding the reduction of joint pain for 66% of the patients treated with 5 g rose hip powder/day compared to 36% of placebo-treated patients; the difference was statistically significant (Rein et al., 2004). A similar double-blind placebo-controlled randomized cross-over study treated 47 OA patients with 5 g rose hip powder/day and 47 patients with placebo. After 3 months, rose-hip resulted in a significant reduction in WOMAC pain score as well as a significant decline in the consumption of ‘rescue medication’ compared to placebo (Winther et al., 2005).

A meta-analysis of these three studies demonstrated that it was twice as likely for an osteoarthritis patient receiving rose hip - compared to a placebo-patient - to responded to the therapy (odds ratio = 2.19; \( p = 0.0009 \)) (Christensen et al., 2008). A cochrane review on rose hip was recently published, evaluating 15 randomized controlled trials on rose hip with 1504 OA patients. The authors reported moderate evidence that *Rosa canina* improved pain and joint stiffness, but not physical function and quality of life (Hu et al., 2018).

Rose hip preparations are well tolerated: In the clinical study by Warholm et al. two patients of 50 taking rose hip (and 2 of 50 taking placebo) suffered from gastrointestinal discomfort, as sole adverse event. Also, years of use of a comparable rose hip preparation in scandinavian countries did not disclose significant data on any adverse events (Warholm et al., 2003). In the cross-over studies by Rein et al. (2004) \((n = 1112)\) and Winther et al. (2005) \((n = 94)\), a few patients experienced acid reflux, “frequent micturition”/“frequent voiding”, diarrhea, constipation, or urticaria. However there were no significant differences between the treatment with rose hip and placebo.

As is known from traditional phytotherapy, combination products may have therapeutic advantages compared to mono-formulations. For rose hip, the first (to our knowledge) placebo-controlled, randomized double-blind study in gonorarthrosis patients with a rose hip combination product was done with a liquid combination of rose hip (*Rosa canina* L.) puree/juice concentrate, nettle (*Urtica dioica* L.) leaf extract, and devil’s claw (*Harpagophyllum procumbens* DC. ex Meisn. or *Harpagophyllum zeyheri* Decne.) root extract, which also supplies vitamin D (special formulation MA212 or Rosaxan). It is a food for special medical purposes according to regulation (EU) No 09/2013 for the dietary management in pain in patients with osteoarthrosis of the knee. Our results indicated outstanding statistical and clinical superiority of this rose hip combination product in comparison to placebo, which was reached in 6 weeks, with further improvement after 12 weeks. This included a significant reduction of all categories of the WOMAC index, as well as significant group differences between MA212 and placebo. The primary endpoint (WOMAC pain score) changed by 29.87 in the MA212 group and by 10.23 in the placebo group \((p_0 < 0.001; p_t < 0.001)\). At the same time, a significant improvement in the quality of life was observed in comparison to placebo - tolerability and safety were excellent (More et al., 2017).

In the following, we discuss the published evidence for the molecular action of rose hip, which can explain the clinical success of MA212 and other rose hip preparations.

*Rosa canina* for the treatment of osteoarthritis – pharmacological evidence

Within the past 2 decades, numerous publications have accumulated regarding the pharmacological effects of *Rosa* species. Altogether, rose hip or preparations thereof act at various levels towards an inhibition of OA. One major mechanism of action is the neutralization of RONS by antioxidative compounds. Furthermore, rose hip reduces OA-specific inflammatory processes, including the reduction of pro-inflammatory cytokines and chemokines, reduction of NF-κB signaling, inhibition of pro-inflammatory enzymes, including COX1/2, 5-LOX and iNOS, reduction of C-reactive protein levels, reduction of chemotaxis and chemoluminescence of PMNs, and an inhibition of pro-inflammatory metalloproteases. Multiple mechanisms act synergistically, targeting RNOS as well as different inflammatory mediators (Fig. 1).

To get a complete picture regarding the molecular mechanism underlying the clinical effects of *Rosa canina* in OA, we performed a literature search in the database Medline; in addition, cited references within published articles on *rosa* species were considered (see Methods section). *Table 1* summarizes the OA-relevant literature for *Rosa canina* describing pharmacological effects:

*Table 2* summarizes and explains the main routes of action of *Rosa canina* in the treatment of OA – antioxidative and anti-inflammatory effects. With the current available data it is difficult to say which of the effects of *Rosa canina* has the largest clinical impact. In addition, different effects will influence each other: the concerted action of different mechanisms by different active components (see below) is what makes *Rosa canina* clinically effective, while each single action by each single compound at the original concentration (as found within a preparation) would likely have negligible effects.

In addition to the routes of action relevant for OA treatment, pharmacological studies with *Rosa canina* or extracts thereof have also been shown to have other beneficial effects, e.g. the reduction of the formation of induced calcium oxalate kidney stones in rats (Tayefi-
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<td>100 µg/ml Rose-hip extract reduced <em>chemotaxis</em> of PMNs. Rose-hip (more efficiently at the higher dose) reduced <em>chemotaxis</em> of PMNs in patients and volunteers – the reduction was approximately 50%. Rose-hip reduced serum CRP levels in patients and volunteers up to 30–35% → anti-inflammatory properties (Clinical improvements in patients) pH-adjusted rose hip extract (from shells) at concentrations of 300–1000 µg/ml inhibited the <em>chemotaxis</em> of PMNs by 35–40%. Chemiluminescence of PMNs was inhibited 27–57% at 2500 µg whole rose hip extract/ml With rose hip: reduced <em>chemotaxis</em> (more that 50% in 12/13 subjects) of PMNs; reduced CRP (27.12%) → anti-inflammatory properties Reduced the level of serum creatinine - enhanced glomerular filtration. Effects were more obvious with the high dose. The extract can inhibit RONS tested in acellular and cellular systems. The IC50 obtained were 5.73 mg/l, 4.34 mg/l and 2.34 mg/l, respectively for O2°−, HOCl and H2O2. For cellular experiments, the IC50 were quite similar. For cellular experiments, the IC50 were quite similar. Thus, the extract did not present an effect on PMN metabolism. Antioxidative effects of <em>Rosa canina</em> are due not only to vitamin C but also to polyphenolics. Inhibitory effects on <em>chemotaxis</em> of human PMNs (but no cytotoxicity)</td>
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<td>The content of the triterpene acids in rose hips is too low to fully explain the clinical effects.</td>
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<td>Murine RAW264.7 macrophage cells stimulated with LPS</td>
<td>Aqueous rose hip extract</td>
<td>Diet with 1% rose hip powder, 21 days</td>
<td>Reduction of LPS-mediated release of IL-6, IL-1beta and TNF-alpha</td>
<td>Autoimmune OA severity, reduction of oxidative stress, and proinflammatory cytokine release</td>
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<tr>
<td>Nadpal et al., 2016</td>
<td>Phenolic profile, vitamin C content, antioxidant potential</td>
<td>Rose hip methanol extract, rose hip purée and jam</td>
<td>In vitro</td>
<td>Quantification of 14 compounds, with quercitrin, gallic acid, and protocatechuic acid as the most dominant - high antioxidant potential of Rosa canina</td>
<td>Anti-inflammatory and anti-cytotoxic activity, with purée of Rosa canina exerting cytotoxic activity against the HeLa cell line - among HeLa, MCF7, HT-29 and MRC-5.</td>
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</table>

The molecular constituents of Rosa canina

A recent review summarizes the phytochemistry of Rosa canina and describes 129 chemical compounds (Ayati et al., 2018). The most prominent compounds/compound groups with health-promoting effects found in rose hip are Ayati et al. (2018), Cheng et al. (2016), Delorman Orhan et al.(2007), Dubtsova et al. (2012), Jimenez et al. (2016), Mihaylova et al. (2018), Nadpal et al. (2016), and Schiewer et al. (2014):

**Phenolics:**
- Phenolic acids (protocatechuic acid, gallic acid, methyl gallate, vanillic acid, syringic acid, chlorogenic acid, cichoric acid)
- Anthocyanins (cyanidin-3-O glucoside)
- Tannins, including proanthocyanidins (condensed tannins)
- Flavonoids (flavone (apigenin), flavonol (rutin, catechin, quercetin, quercitrin), flavanone (hesperidin, eriodictyol, taxifolin), dihydrochalcone (phloridzin) derivatives)
- Sterols (beta-sitosterol)

**Terpenoids:**
- Pentacyclic triterpenes (ursolic acid and oleanolic acid)

**Other:**
- Fruit acids (ascorbic, malic, citric acids)
- Fatty oils (α-linolenic, linoleic, palmitic acids)
- Pectins
- Carotenoids (lycopenes, beta carotene), tocopherols
- Galactolipids (GOPO/GLGPG, Mono-galactosyl diglyceride, di-galactosyl diglyceride)

Many of the above compound-groups or compounds have antioxidant potential (Fig. 1). Accordingly, the above-mentioned rose hip product Rosaxan (special formulation MA212) supplies ≥ 30 mg vitamin C per daily dose. However, the antioxidant activity of Rosa canina does not only stem from the high amount of vitamin C, but also from a rich content of phenolic acids, proanthocyanidins, flavonoids, vitamin E and carotenoids, but also from a rich content of phenolic acids, proanthocyanidins, flavonoids, vitamin E and carotenoids [4, 75]. The ability of rose hip in scavenging H2O2 was found to be comparable to that of the antioxidant BHA (butylated hydroxyanisole) (Yilmaz and Ercisli, 2011).

In addition, numerous anti-inflammatory effects have been described (Table 2), which can be attributed to the synergistic action of many of the numerous rose hip compounds. For many of these compounds, first insights into the molecular anti-inflammatory mechanism have been gained.

For example: Methyl gallate has a dual cyclooxygenase-2/5-lipooxygenase inhibitory activity (Kim et al., 2006). The triterpenoid ursolic acid, suppresses NF-κB, AP-1 and NF-AT (Checker et al., 2012). The flavonoid quercetin was found to attenuate mitochondrial dysfunction.
Antioxidative effects (RONS – neutralization) / Containing potent antioxidants

Reduced production of pro-inflammatory cytokines TNFα, IFN-γ, IL-1β, IL-6, IL-8, IL-12, and chemokines CCLS/RANTES, CCL11/IL-10, macrophage inflammatory proteins MIP-2 and MIP-3α

Inhibition of NF-κB signaling

Inhibition of pro-inflammatory enzymes COX1, COX2, 5-LOX, 12-lipoxygenase (also by Rosa canina-derived linoleic acid)

Inhibition of prostaglandin E synthase expression

Inhibition of iNOS² /NO production

Reduction of the serum level of the inflammatory marker C-reactive protein (CRP).

Reduction of chemotaxis and chemoluminescence of PMNs

Inhibition of pro-inflammatory metalloproteases, e.g. matrix metalloproteinases MMP-1, -8, -9, -13; aggrecanase ADAMTS-4iso

Table 2:

Routes of action by Rosa canina preparations in the treatment of OA.

<table>
<thead>
<tr>
<th>Effect by Rosa canina</th>
<th>References (see also Table 1)</th>
<th>Explanation</th>
</tr>
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<tbody>
<tr>
<td>Antioxidative effects (RONS – neutralization) / Containing potent antioxidants</td>
<td>(Ayati et al., 2018; Böhm et al., 2003; Daels-Rakotoarison et al., 2002; Jimenez et al., 2016; Lattanzio et al., 2011; Nadpal et al., 2016; Turkben et al., 2010; Yilmaz and Ercoli, 2011)</td>
<td>RONS are signaling molecules for the inflammatory-proliferative response (Boehme and Rolauffs, 2018). ROS overproduction damages extracellular matrix components and causes apoptosis (Li et al., 2012; Satipornpalangkal et al., 2009). Pro-inflammatory cyto-chemokines stimulate catabolic signaling and the inflammatory response and thereby lead to the progression of OA (Gao et al., 2015; Jovanovic et al., 2012; Kalaziszynska et al., 2017; Latoute et al., 2017). On a molecular level this includes activation of the NF-κB pathway (Lepeut et al., 2018). The cyto-chemokines derived from adipose tissue pose an additional risk factor for OA (Wang and He, 2018). The transcription factor NF-κB is overexpressed in active OA in response to inflammatory cytokines (Lepeut et al., 2018). NF-κB in turn induces iNOS, as well as matrix metalloproteases (Zheng et al., 2017). COX-1, COX-2 and 5-LOX are part of the arachidonate metabolism and lead to the production of inflammation mediators (Hinz and Brune, 2004). Prostaglandin E synthase mediates the production of pro-inflammatory prostaglandins. The enzyme iNOS synthesizes NO, which is in turn serves as inflammatory second messenger to indirectly upregulate WNT signaling (Zhong et al., 2017) which in turn leads to the induction of matrix metalloproteases and aggrecanases (De Santis et al., 2018). An elevated serum CRP level is not only a marker for inflammation. It also is a risk factor for OA (Suysa et al., 2018), as well as for as well as periarticular joint infection (Xu et al., 2018). In mice on a high-fat diet, human CRP aggravated osteoarthritis development (Kozijn et al., 2019). Chemotaxis of PMNs furthers the transportation of immune cells into tissue, furthering inflammation (Stanczyk et al., 2005). Matrix metalloproteases and aggrecanases break down collagen and aggrecan, furthering cartilage destruction (Cawston and Young, 2010; Troeberg and Nagase, 2012). Verma and Dalal, 2011; Yang et al., 2017)</td>
</tr>
</tbody>
</table>

Inhibition of NF-κB signaling | (Schwager et al., 2011; Shakiabi et al., 2012) | |

Inhibition of pro-inflammatory enzymes COX1, COX2, 5-LOX, 12-lipoxygenase (also by Rosa canina-derived linoleic acid) | (Jager et al., 2007; Nadpal et al., 2016; Shakiabi et al., 2012; Wenzig et al., 2008) | |

Inhibition of prostaglandin E synthase expression | (Schwager et al., 2011) | |

Inhibition of iNOS² /NO production | (Park et al., 2014; Schwager et al., 2011) | |

Reduction of the serum level of the inflammatory marker C-reactive protein (CRP). | (Kharazmi and Winther, 1999; Willich et al., 2010; Wünther et al., 1999) | |

Reduction of chemotaxis and chemoluminescence of PMNs | (Kharazmi and Winther, 1999; Larsen et al., 2003; Wünther et al., 1999) | |

Inhibition of pro-inflammatory metalloproteases, e.g. matrix metalloproteinases MMP-1, -8, -9, -13; aggrecanase ADAMTS-4iso | (Park et al., 2014; Schwager et al., 2011; Schwager et al., 2014; Shakiabi et al., 2012) | |

* Also by Rosa canina-derived galactolipids – effects in macrophages, peripheral blood leukocytes and/or chondrocytes.

** Based on published experimental data with statistically significant or clearly apparent effects.

by upregulating adenosine monophosphate-activated protein kinase/protectin D1 signaling (Qiu et al., 2018). The flavonoid kaempferol (derivatives thereof are also found in Rosa canina (Ayati et al., 2018)) was found to suppress the MAPK related ERK and P38 pathways, resulting in inhibition of COX2, iNOS and metalloproteinase expression (Huang et al., 2018). Astragalin (also found in Rosa canina) (Ayati et al., 2018) was found to inhibit NF-κB (Kim and Kim, 2011). Linoleic- and α-linolenic acids from rose hip were found to inhibit COX-1 and COX-2 (Jager et al., 2008). In human articular chondrocytes, cyanidin-3-O-glucoside was found attenuate matrix metalloproteinase induction; also it inhibited the degradation of the NF-κB inhibitor α (IkBa), modulated the phosphorylation of the NF-κB subunit p65, and inhibited the ERK/MAPK pathway (Wongwichai et al., 2019).

Conclusion

Rose hip contains numerous compounds which are known for their health-promoting effects. More specifically, Rosa canina preparations display potent antioxidant radical scavenging effects as well as anti-inflammatory activities, which counteract OA. Anti-inflammatory activities include the reduction of pro-inflammatory cytokines and chemokines, reduction of NF-κB signaling, inhibition of pro-inflammatory enzymes, including COX1/2, 5-LOX and iNOS, reduction of C-reactive protein levels, reduction of chemotaxis and chemoluminescence of PMNs, and inhibition of pro-inflammatory metalloproteases. In addition, Rosa canina was shown to regulate blood lipids and counter obesity, with indirect beneficial effects against OA.

Along this line, efficacy of Rosa canina preparations is demonstrated in several controlled clinical studies in patients with OA, with excellent tolerability.

Further research is needed to elucidate how and in which manner single compounds interact e.g. with specific proteins within the cellular signaling cascades in chondrocytes.

The signaling cascades e.g. of the NF-κB pathway are well described (Liu et al., 2017), for example it is known that in OA, USP14-mediated 1xβα degradation exacerbates NF-κB activation and IL-1β-stimulated chondrocyte dedifferentiation (Li et al., 2019). However, although it was found that cyanidin-3-O-glucoside (one of the active constituents of Rosa canina) inhibits the degradation of 1xβα (Wongwichai et al., 2019), it is not known how exactly this is achieved on a molecular level.

Similarly, a Rosa canina derived galactolipid was shown to reduce iNOS mRNA levels as well as lower the expression of several inflammatory cytokines and chemokines, possibly via elements of the NF-κB pathway (Schwager et al., 2011), however, molecular details including binding partners remain to be elucidated.

In the future, it may also be possible to evaluate – in pharmacokinetic studies – the actual systemic and chondrocyte-specific availability...
of *Rosa canina*-derived compounds following oral the intake of clinically successful *Rosa canina* preparations. It is likely that these available compounds - including also metabolic derivatives of the administered compounds - achieve the observed effects as a whole.

Conflict of interest

J. Gruenwald is shareholder of MedAgil (distributor of the Rose hip product Rosaxan) via his shares in Phytopharm Consulting GmbH. R. Uebelhack has no conflict of interest. M. Moré is affiliated with Herbalist & Doc Gesundheitsgesellschaft mbH, Berlin, Germany (CEO Joerg Gruenwald). She is also an independent medical writer, and was paid for writing this article by medAgil Gesundheitsgesellschaft mbH.

References


