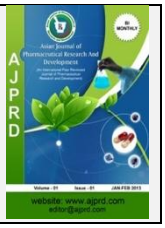
Available online on 15.2.2025 at http://ajprd.com

Asian Journal of Pharmaceutical Research and Development

Open Access to Pharmaceutical and Medical Research



Open Access

Review Article

The Role of *Rosa Canina* in Modulating NF-Kb and MAPK Signaling Pathways: A Key to Anti-Inflammatory Therapy

Sandip Tejpal*, Samridhi Dogra, Sachit Sharma

Department of Pharmaceutical Sciences, Guru Nanak Dev University, Amritsar, Punjab, India

A B S T R A C T

Rosa canina L., which is more commonly known as rosehip, has become a plant of great scientific interest due to its nutritional, cosmetic, and therapeutic applications. This review study highlights the fact that the high levels of vitamins, carotenoids, tocopherol, and phenolic acid in this substance are responsible for its anticarcinogenic, hepatoprotective, antioxidant, and anti-inflammatory properties. The German Commission E published a negative monograph on rose hip, rose hip and seed, and rose hip seed due to insufficient evidence of their effects and usefulness. As a result, a literature review was conducted to outline the pharmacological and clinical effects of *Rosa canina* L. in order to re-evaluate its usefulness in traditional medicine. Several rose hip and rose hip and seed formulations have been demonstrated to offer antioxidant and anti-inflammatory effects. Such action mechanisms involve lipophilic components. Litozin, a proprietary powder made from rose hips and seeds, has been shown to be beneficial in treating patients with osteoarthritis, rheumatoid arthritis, and low back pain in several exploratory investigations. In addition to vitamin C, a number of the components found in rose hips possess strong antioxidant and radical scavenging activities. The pharmacological and clinical effects that were found can be explained by a number of different components, including as phenolics, terpenoids, galactolipids, carotenoids, fruit acids, and fatty oils. In addition, anti-inflammatory effects include lowering the levels of pro-inflammatory cytokines and chemokines, NF-kB signalling, pro-inflammatory enzymes (COX1/2, 5-LOX, and iNOS), C-reactive protein levels, PMN chemotaxis and chemoluminescence, and pro-inflammatory metalloproteases.

Keywords: *Rosa canina*, NF-κB, MAPK, Anti-oxidant, Anti-inflammatory

A R T I C L E I N F O: Received 19 Nov.2024; Review Complete 29 Dec. 2024; Accepted 26 Jan. 2025. ; Available online15 Feb. 2025

Cite this article as:
Tejpal S, Dogra S, Sharma S, The Role of Rosa Canina in Modulating NF-Kb and MAPK Signaling Pathways: A Key to Anti-Inflammatory Therapy, Asian Journal of Pharmaceutical Research and Development. 2025; 13(1):128-137,
DOI: http://dx.doi.org/10.22270/ajprd.v13i1.1516

*Address for Correspondence:
Sandip Tejpal, Department of Pharmaceutical Sciences, Guru Nanak Dev University, Amritsar, Punjab, India

INTRODUCTION

In response to harmful stimuli such as viruses, damaged cells, toxins, or radiation, the immune system produces inflammation, which eliminates the harmful stimuli and initiates the healing process. As a result, inflammation is a crucial defensive mechanism for maintaining healthy health [1]. In general, cellular and molecular interactions and processes that occur during acute inflammatory reactions significantly reduce the chances of injury or infection. This mitigation mechanism causes the initial inflammation to go down and tissue homeostasis to be restored. However, if acute inflammation is not controlled, it can evolve into chronic inflammation, which can lead to a number of inflammatory diseases. Inflammation is a secondary defensive process that assists the body in dealing with pathogens. The reactions that inflammation induces are one of the most significant parts of pathophysiology [2]. Inflammation is largely dependent on the reactions of the immune system, which include both cellular and humoral responses. As this exercise illustrates, inflammation has an effect on two of the leading causes of mortality and disability around the world: cardiovascular disease (CVD) and cancer.

It has been more than forty years since NF-κB signalling was first discovered. The initial recognition of the role of NF-κB signalling in mediating inflammatory responses occurred. However, research has demonstrated that its function can be expanded to include a variety of signalling pathways, biological processes, human illnesses, and therapeutic options. The complicated role of NF-κB signalling in inflammation, immunological regulation, and the tumour microenvironment is also discussed, along with its physiological and pathological stages. In addition, we show

how NF-κB signalling is involved in a variety of human diseases, including cancers, inflammatory and autoimmune disorders, cardiovascular diseases, metabolic diseases, neurological diseases, and COVID-19 [3]. Next, we discuss the treatment techniques that are designed to target NF-κB signalling. These include IKK inhibitors, monoclonal antibodies, proteasome inhibitors, DNA binding inhibitors, TKIs, non-coding RNAs, immunotherapy, and CAR-T. Finally, we offer a proposed route for future research on NF-κB signalling.

The NF-κB transcription factor family plays a significant role in numerous physiological and pathological processes, and it also plays a significant role in a multitude of other activities. There are two separate NF-κB routes, namely the canonical and non-canonical pathways. These pathways are activated by different mechanisms. It is well known that the canonical NF-κB, which is involved in inflammation, immunological response, cell proliferation, differentiation, and survival response, is activated by a wide variety of various external stimuli [4]. One of the most important steps in the process of classical NF-κB functioning is the activation of the IKKs (IκB kinases) complex, which is dependent on phosphorylation. Because of this, the proteins that inhibit IκB go through a process of phosphorylation, and then they are degraded by the proteasome, which is a process that is dependent on ubiquitination. The release of the κB transcription factor and its subsequent movement to the nucleus, where it has the potential to activate the genes that it was designed to activate, is made possible by this. Due to the fact that NF-κB also brings about the development of negative regulators such IκBα, A20, and p105, which results in the formation of a negative feedback system, the activation is not only transient but also ephemeral. The activation of non-canonical NF-κB, on the other hand, takes place through a limited number of TNF superfamily receptors, which suggests that the biological tasks that are played by this pathway subset are more specifically focused. NIK, which stands for NF-κB-inducing kinase, remains below the detectable level in the steady-state situation. This is because the degradation that occurs in this route is mediated by ubiquitination and is dependent on TRAF3. Activation of the cellular inhibitor of apoptosis, also known as E3 ubiquitin ligase cIAP, results in the degradation of TRAF3, which in turn leads to the accumulation of NIK."14" Following the phosphorylation of p100 by NIK and IKKα, the RelB/p52 dimer is released through a process that allows it to translocate into the nucleus for the purpose of activating the target gene. The proliferation of immune cells in many layers is a phenomenon that can be traced to the non-canonical NF-κB pathway. An example of this would be the thymus epithelial cells (TECs), which are essential for the development of T-cells and, without this pathway, they are unable to mature and perform their functions correctly. It is also generally accepted that this route is responsible for regulating the development of the secondary lymphoid organ, also known as the SLO. While this is going on, research indicates that this pathway is extremely important for the development of chronic inflammatory diseases and tertiary lymphoid organ (TLO) inflammation [5].

One example of a complex network of interconnected signalling cascades is the mitogen-activated protein kinase (MAPK), which has a role in the progression of tumours, the formation of cancer, and the resistance of tumours to therapy. Targeting members of the MAPK family of kinases has resulted in the development of a variety of therapies that are specifically designed to treat cancer. One of the issues that is now being faced is resistance to MAPK inhibitors. The primary reason for this is the high number of interactions, as well as the possibility of compensating responses. In this review, we will discuss all of the cancer-related repercussions that are associated with MAPK pathways, with a particular focus on the manner in which MAPK interaction with significant signalling pathways in pathological states influences the signalling patterns of tumours [6].

Rosa canina

In recent years, there has been a growing desire for herbal treatments, which has resulted in a multitude of studies being conducted to investigate the traditional therapeutic use of various plants. One of these plants is *Rosa canina* L., more frequently referred to as the "dog rose," and the concentrate of this review is on the bioactive components that are known to be present in the plant. In view of the fact that being overweight is associated with an increased risk of developing osteoarthritis, which is the most prevalent joint ailment on a global scale, the purpose of this study is to identify whether or not the plant possesses anti-inflammatory properties and whether or not any of its elements have an effect on obesity. This article will devote a significant amount of space to describing the *R. canina* pseudo fruits, which are more commonly referred to as "fruits" in the medical literature [7]. Aggregate fruits, also known as rose hips, are those that include a significant quantity of achenes, which are the actual fruits that carry seeds. Moreover, they have a flower cup, also known as a hypoanthium, that is larger, redder, and fleshier. There are other rose varieties that do produce rose hips, but only rose hips from *R. canina* have been proved to have therapeutic properties. This information has been brought to the attention of the authors [8]. The use of *R. canina* for therapeutic purposes has been documented for at least two millennia, according to sources. Numerous hypotheses have been proposed due to the fact that this plant family contains a large number of subspecies and that numerous assertions have been made on the potential health advantages of the plants. *R. canina* possesses a number of characteristics and components, some of which are as follows: first, anti-inflammatory substances; second, flavonoids; third, carotenoids; fourth, high vitamin content, particularly vitamin C; and fifth, antioxidant qualities [9].

More than a hundred different species are found within the Rosa genus, with the majority of those species' distributions being centred in the regions of the Americas, Europe, Asia, and the Middle East. It is well knowledge that the dog rose, also known by its scientific name Rosa canina L., is a shrub that has upright branches that can bend or arch up to a height of 3.5 meters (and even climb). White to a very light pink is the most common colouration for the petals; a very dark pink colouration is extremely uncommon [10]. The ripening of the fruit occurs later on. Extensive documentation of the biochemistry and biology of Rosa canina L. has been compiled from a wide variety of sources, including botanical, agrotechnical, chemical composition, and plant uses. Over the course of many centuries, the fruits of the *Rosa canina* L. tree were utilised in a wide variety of traditional diets and

therapeutic practices. Rose hips are utilised in a variety of culinary applications, including but not limited to the following: juice, wine, tea, jelly, jam, and a combination with dried salmon eggs. An important characteristic of *Rosa canina* L. is that it contains a significant amount of phenolic compounds. According to the findings of the research, these compounds have the ability to inhibit actions related to carcinogenesis, mutagenesis, and antioxidants [11]. According to the findings of several studies, polyphenol molecules have the potential to shield persons from illness and even perform the function of antioxidants.

Figure 1: *Rosa canina* plant

Taxonomy

Kingdom	Plantae
Clade	Angiosperms
Order	Rosales
Family	Rosaceae
Genus	Rosa
Species	*Rosa canina*

Traditional uses

In many different nations, the dog rose, also known as *Rosa canina*, has become an essential component of traditional medicine due to its numerous applications in the fields of medicine, culinary arts, and practical applications [12]. Since ancient times, the medicinal fruit of this plant, known as rose hips, has been utilised as a remedy to fortify the immune system and protect against illnesses such as the common cold and influenza. This is due to the high concentration of vitamin C that it contains. To compensate for the scarcity of citrus fruits that contained vitamin C during World War II, rose hip syrup was produced in the United Kingdom. Inflammation and soreness in the joints, particularly in cases of gout and arthritis, were also alleviated by the usage of rose hips. Additionally, rose hips were utilised to promote digestive health by alleviating cramps and diarrhoea. Along with alleviating respiratory difficulties such as coughs and bronchitis, rose hip decoctions, which are a type of diuretic, also helped with the process of detoxification [13]. An additional traditional treatment for skin irritations and wounds was the application of rose hips and petals to the

affected area of the skin. In the realm of culinary applications of *Rosa canina*, rose hip syrups, jams, and jellies are highly respected due to their acidic flavour and the extensive nutritional benefits they offer. In certain regions, rose hips were fermented into wines or cordials, and in others, dried petals and hips were regularly steeped into herbal teas. Both of these processes were rather common. Infusions of rose petals are used as a natural conditioner to promote shine in hair, and rosehip oil, which is produced from the seeds of roses, is used to moisturise the skin, reduce scars, and combat dryness. These are just two of the traditional cosmetic uses for roses [14]. Within the realm of folklore, *Rosa canina* was held in high esteem due to its symbolic and practical applications, as it was believed to protect against malevolent spirits. For the purpose of preserving cattle and property, it was common practice to plant its prickly bushes as natural hedges. In addition, during times of famine, the seeds and fruit of this plant were utilised as a source of nutrition for animals. As evidenced by the wide range of applications mentioned above, *Rosa canina* serves a variety of cultural and medicinal functions [15].

Bioactive compounds of *Rosa canina*

The rosehip plant, which is a member of the Rosaceae family and is known by its scientific name *Rosa canina* L., is undergoing explosive development in many regions of the world. People have relied on the numerous use of this plant for as long as they can remember, including its culinary and medical applications. Indigestion, infections, and fever are all conditions that can be alleviated with the use of rosehip in traditional European medicine. One of the reasons why rosehip has such a positive impact on one's health is that it includes a large quantity of bioactive components. These substances include vitamins, minerals, antioxidants, and phenolic compounds. Rosehip is equipped with a multitude of bioactive components, which encompass phenolic acids, carotenoids, tannins, tocopherols, α- and β-tocopherols, p-coumaric acid, ellagic acid, caffeic acid, lycopene, and zeaxanthin. The canine rose hips, also known as Cynosbati fructus, contain a wide variety of nutrients, including sugars, organic acids, pectins, tannins, carotenoids, fatty acids, vitamins (particularly vitamin C and vitamins B1, B2, K, PP, and E), macro- and microelements, and more. Research was conducted to investigate the nutritional composition and technological properties of Rosa canina L. fruits, which are also referred to as rosehips [15]. This was done in order to investigate the potential applications of these fruits. Rose hips are claimed to have a vitamin C concentration that is substantially higher than that of citrus fruits, according to papers obtained from scientific journals. With a vitamin C content that ranges from 30 to 1300 mg/100 g, rose hips are well recognised as having the highest concentration of vitamin C among fruits and vegetables. Furthermore, rose hips include a number of elements, including minerals, vitamins, carotenoids, tannins, pectin, sugars, organic acids, amino acids, essential oils, and fruit acids. Both indigenous traditional knowledge and western study have brought to light the fact that it has the potential to offer significant nutritional and therapeutic benefits among natural antioxidants [16].

NF-κβ signaling pathway

As a result of the comprehensive examination of the role that NF-κB plays in the expression of other proinflammatory genes, including cytokines, chemokines, and adhesion molecules, as well as its activation by proinflammatory cytokines like interleukin 1 (IL-1) and tumour necrosis factor α (TNFα), it has been widely recognised as a prototypical proinflammatory signalling pathway for a considerable amount of time. Because inflammation is a complex physiological process, it is not possible to deduce the function of NF-κB in the inflammatory response based on research that were conducted in vitro. The purpose of this article is to provide an explanation of the complex activities that the NF-κB pathway plays in inflammation, as demonstrated by genetic data obtained from mice.

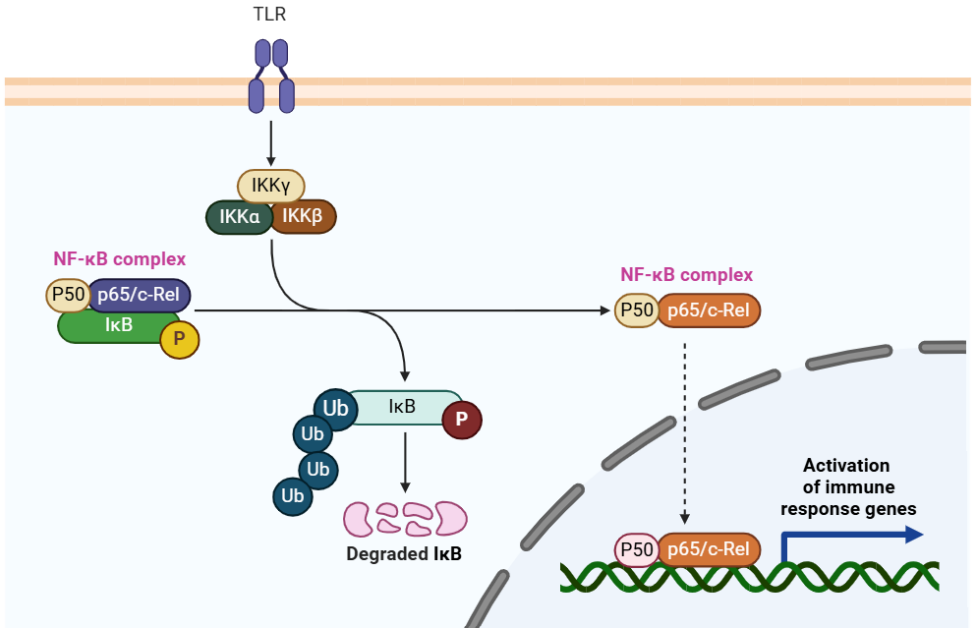


Figure 2: NF-κβ signaling pathway

Activation of NF-κβ in inflammation

The family of inducible transcription factors known as nuclear factor-κB (NF-κB) is responsible for controlling a number of genes that are involved in many aspects of the immune and inflammatory responses. Members of this structurally related family include the transcription factors NF-κB1 (also known as p50), NF-κB2 (also known as p52), RelA (also known as p65), RelB, and c-Rel. All of these transcription factors perform a similar function. Their ability to mediate the transcription of target genes is achieved through their binding to a particular area of DNA known as the κB enhancer, which can take the form of hetero- or homo-dimers on the DNA. A group of proteins known as inhibitory proteins are responsible for maintaining the presence of NF-κB proteins within the cytoplasm. Among the members of this family are those belonging to the IκB family, as well as proteins that are related to them and include ankyrin repeats. Up to this point, IκBα has been the member of the IκB family that has been subjected to the most thorough investigation and has had the most significant impact. Furthermore, it is worth noting that NF-κB1 and NF-κB2 precursor proteins, namely p105 and p100, also perform the role of IκB-like proteins [17]. This is because their C-terminal part is structurally comparable to that of IκB, and it is responsible for inhibiting NF-κB. In spite of the fact that their signalling methods are distinct, the canonical and noncanonical pathways, also known as alternative pathways, hold major importance in the regulation of immunological and inflammatory responses. Furthermore, they play a role in the activation of NF-κB. A wide variety of stimuli, including ligands from various cytokine receptors, pattern-recognition receptors (PRRs), members of the TNF receptor (TNFR) superfamily, T-cell receptors (TCRs), and B-cell receptors, are responsible for activating the canonical NF-κB pathway [18]. One of the primary mechanisms by which traditional NF-κB activation takes place is when a complex of multi-subunit IκB kinase (IKK) phosphorylates IκBα at certain locations, hence inducing its inducible breakdown by causing its degradation. A total of three components, namely IKKα, IKKβ, and NF-κB essential modulator (NEMO) or IKKγ, are responsible for the formation of IKK. Catalytic subunits are the first two elements of the structure. In addition to cytokines, growth factors, mitogens, microbiological components, and stress agents, there are a variety of stimuli that have the potential to activate IKK. In the process of activation, IKK phosphorylates IκBα on two serines located at the N-terminal region. Through this process, the proteasome is able to destroy IκBα in a manner that is dependent on ubiquitin. As a consequence of this, classical members of NF-κB, specifically the p50/RelA and p50/c-Rel dimers, undergo a rapid and short translocation to the nucleus [19].

Role of *Rosa canina* in suppressing NF-κβ activation

As a result of its significant function in suppressing NF-κB activation, Rosa canina possesses significant therapeutic potential for the management of immune-related diseases and inflammation. The pathway known as NF-κB is responsible for regulating the expression of genes that are associated with inflammation. These genes include cytokines, such as TNF-α and IL-6, chemokines, and enzymes like COX-2 [20]. The IκB kinase (IKK) complex is responsible for phosphorylating and degrading IκB proteins in order to be able to activate NF-κB. Because of this, NF-κB is able to enter the nucleus and initiate the inflammatory response. There are bioactive chemicals found in *Rosa canina*, including quercetin, ellagic acid, and other polyphenols. These molecules have the ability to directly inhibit the IKK complex, which in turn prevents the phosphorylation and degradation of IκB receptors. As a result of this inhibition, NF-κB is prevented from being released and instead remains confined to the cytoplasmous compartment [21].

In addition, the antioxidants that are abundant in *Rosa canina*, including as vitamin C, carotenoids, and flavonoids, have the ability to decrease the activity of reactive oxygen species (ROS), which are known to play a key role in the activation of nuclear factor κB. It is through the reduction of oxidative stress that *Rosa canina* is able to suppress the activation of the IKK complex as well as oxidative stress. Through the suppression of upstream pro-inflammatory cytokines such as TNF-α and IL-1β, *Rosa canina* also has the ability to diminish the signals that activate NF-κB within the body. Several of its bioactive compounds have the ability to directly disrupt the nuclear translocation of NF-κB [22]. This is accomplished by inhibiting its capacity to bind to DNA and activate genes that are involved in inflammation. Through the establishment of a negative feedback loop, *Rosa canina* plays a role in the regulation of chronic inflammation by reducing the synthesis of inflammatory mediators. This impact is achieved by targeting several steps in the NF-κB pathway. Because of these qualities, it has the potential to be utilised as an all-natural anti-inflammatory drug for the management of disorders such as inflammatory bowel disease, arthritis, and other conditions that involve the continuous activation of NF-κB [23].

- **Inhibition of IKK complex:** Inhibiting the IKK complex is a crucial strategy for lowering NF-κB activation. This is due to the fact that the IKK complex is extremely important for the management of NF-κB activation, as well as for the regulation of inflammation and different immune responses. Targeting the IKK complex is one method that can be utilised to alleviate the production of genes that promote inflammation. Because of this, the phosphorylation and degradation of IκB proteins will be restricted, which will, in turn, block the release of NF-κB and its translocation into the nucleus. Additionally, *Rosa canina* includes naturally occurring compounds that interfere with the ATP-binding sites of the IKK complex, thereby directly reducing the catalytic activity of the complex. The compounds quercetin and ellagic acid are included in this category. By neutralising reactive oxygen species (ROS), the antioxidants found in Rosa canina, such as vitamin C and carotenoids, further limit the activity of the IKK complex. This dual mechanism is responsible for inhibiting the NF-κB signalling cascade and stabilising IκB proteins. The inhibition of the IKK complex has the potential to be a therapeutically useful approach, particularly for the treatment of autoimmune disorders, cancers, and chronic inflammatory diseases. Through the suppression of IKK activity, *Rosa canina* demonstrates potential as a natural anti-inflammatory and immune-modulating medication. This is only one of the numerous ways that Rosa canina demonstrates [24].

- **Oxidative stress reduction:** The presence of reactive oxygen species (ROS) is a crucial element in the process of NF-κB signalling. *Rosa canina* contains a high concentration of antioxidants, including vitamin C, carotenoids (beta-carotene, lycopene), and flavonoids. These antioxidants aid to reduce oxidative stress by scavenging reactive oxygen species (ROS). *Rosa canina* has the ability to neutralise reactive oxygen species (ROS), hence reducing the activation of the IKK complex and NF-κB [25].
- **Upstream cytokine signaling modulation:** The NF-κB pathway is primarily activated by pro-inflammatory cytokines such as TNF-u03b1 and IL-1u03b2, which are considered crucial activators. *Rosa canina* has the ability to inhibit the manufacture of these cytokines, which in turn reduces the activation of NF-κB. This is accomplished by lowering the stimulation of upstream receptors and signalling molecules. Consequently, this following consequence has the effect of inhibiting the inflammatory cascade [26,27].

MAPK signaling pathway

Mitogen-activated protein kinase (MAPK), which has a role in the progression of tumours, the genesis of cancer, and the resistance of tumours to medicine, is an example of a complex network of interconnected signalling cascades. Targeting members of the MAPK family of kinases has resulted in the development of a variety of therapies that are specifically designed to treat cancer. One of the issues that is now being faced is resistance to MAPK inhibitors. The primary reason for this is the high number of interactions, as well as the possibility of compensating responses [28]. One of the most important roles that the mitogen-activated protein kinase (MAPK) pathway performs is in the process of transitioning from responses that occur outside of cells to those that occur inside of cells. The anomalies in signalling cascades that are caused by epigenetic and genetic alterations distinguish cancer from other diseases. Cancer is one of the diseases that falls into this category [29]. There have been a number of investigations conducted on the homeostatic and pathologic conduct of MAPK signalling; however, there is still a great deal that is not explained in terms of regulation and action models in both preclinical and clinical research. It is important to note that MAPK is involved in the response to cancer treatment, more specifically in the activation of compensation mechanisms following the inhibition of MAPK through experimental means. MAPK is a multi-faceted cell signalling system that plays a role in maintaining cellular homeostasis, reacting to cancer treatments, and activating compensatory pathways [30]. The current work investigates a new understanding of MAPK as a cell signalling system. A significant number of MAPK inhibitors are responsible for the activation of compensatory feedback loops in cancer cells and components of the tumour microenvironment, which ultimately leads to the development of resistance. In the treatment of cancer, the utilisation of new combinatorial drugs is required in order to cut down on the activation of alternative pathways [31]. This will make it possible to generate novel pharmaceuticals that are founded on the incorporation of findings from translational research, which will result in the development of new medications.

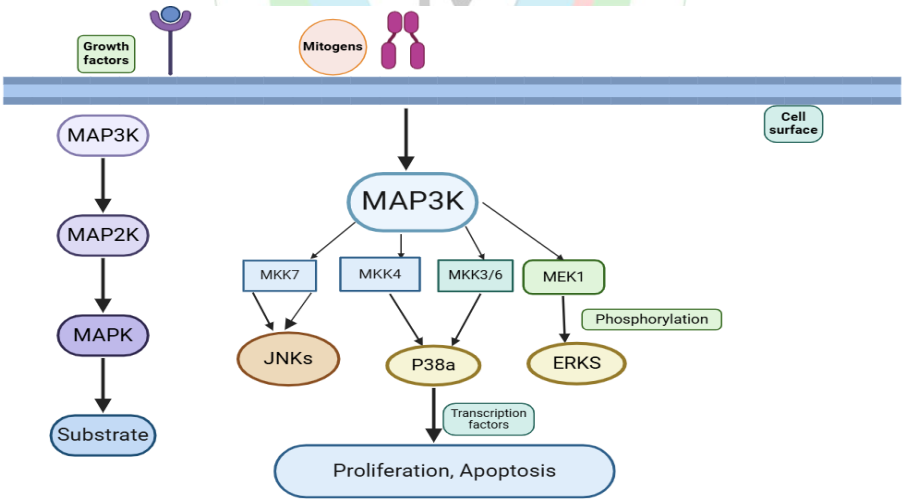


Figure 3: MAPK signaling pathway

Physiological roles of MAPK signaling pathway

Regulatory factors are activated in a manner that is analogous to turning on a switch, and the structure of a signalling cascade such as MAPK is complex, consisting of a multitude of pathways that interact with one another and are continually talking with one another. If one were to investigate the MAPK pathways, it would be discovered that these routes magnify essential molecules that are necessary for the growth, proliferation, and survival of cells [32]. The MAPK signalling cascade is built on the foundation of the interaction that occurs between growth factors (GFs) and the growth factor receptors (GFRs) that are specific to certain growth factors. A typical situation involves GFs binding to transmembrane glycoproteins belonging to the RTK family [33]. This, in turn, activates the signal transduction cascade, which, in turn, causes signal transduction through cytosolic intermediates and, eventually, the regulation of effector gene transcription and translation. Out of all of these, growth factor receptors stand out due to the fact that they play a significant role in enabling signal transduction downstream following activation. Take for example the situation of epithelial growth factor (EGF), which attaches to its particular receptor on the cell membrane (EGFR, which stands for epidermal growth factor receptor on the cell

membrane). More than 150 small G-proteins, such as HRAS, KRAS, and NRAS, are members of the RAS superfamily of GTPases [34]. These GTPases serve as the initial set of cytosolic intermediates that launch the phosphorylation cascade that occurs in the MAPK pathway. Following the activation of EGFR, the EGFR-associated nucleotide exchange factor, also known as SOS1, contributes to the activation of the RAS GTPase. SOS works as a limiting condition for the creation of RAS-GTP, which is the active form of RAS. It is responsible for determining how quickly GTP is converted into GDP. Because it is the downstream effector of RAS, RAF is dependent on the contact with an activated RAS in order to function properly [35]. In order to facilitate the progression of the pathway, various members of the RAF family, such as ARAF, BRAF, and CRAF, are serine/threonine kinases. These kinases activate MAP kinase-ERK kinase (MEK) and Extracellular signal-regulated kinases (ERK1/2), which in turn helps to advance the system. First, the Mitogen-activated protein kinase kinases (MAPKK) (RAF and variants) are involved in the activation cascade. Next, the MAPK kinase (MAPKK: MEK1/2/3/4/5/6/7) is involved, and finally, the MAPK itself is involved. There are three basic classical MAPKs, each of which has its own unique isoform. These are ERKs, which include ERK1 and ERK2 isoforms; JNKs, which are c-Jun N-terminal kinases, with JNK1, JNK2, and JNK3 isoforms; and p38 MAPKs, which comprise p38α, p38β, p38γ, and p38δ isoforms. Among the many processes in which these kinases are involved, three of the most important ones are cell survival, proliferation, and differentiation [36]. The phosphorylated targets of MEK and ERK1/2, respectively, are crucial for these three processes. The phosphorylation targets of ERK1/2 are highly varied, and this is true regardless of the compartment or location of the cell. Some of the transcription factors that can be activated by Erk1/2 are CREB, c-Myc, nuclear factor kappa B, and transcriptional regulator Myc-like. Erk1/2 is able to activate these transcription factors in the nuclease. Because of this, ERK1/2 is a target that shows great promise for the therapy of malignant malignancy [37]. The architecture of complimentary signalling pathways is comparable to that of MAPK pathways. This means that all of these pathways begin with contact with an external stimuli (such cytokines or GFs), and they all terminate in the translocation of certain components into the nucleus, which enhances gene expression. Other significant pathways that are associated with the regulatory activity of the MAPK pathway include the signalling pathways of P13k/AKT/mTOR (phosphoinositide-3-kinase/v-akt murine thymoma viral oncogene homolog 1/mechanistic target of rapamycin kinase) and TGFβ (transforming growth factor beta). These pathways involve varying degrees of interaction and cumulative signal transduction [38]. The nuclear translocation of MAPK signalling components, which might be regarded as an essential regulatory system of critical cellular functions, is one of the prospective therapeutic interventions that could be utilised.

Role of *Rosa canina* in suppressing MAPK signaling pathway

Rosehips are a type of extract that can be obtained from either Rosa canina or Rosa villous, which are both members of the Rosaceae family. Rosehips are derived from the rose plant. The anti-inflammatory and alternative treatment for osteoarthritis capabilities of rosehip extracts have been the subject of a significant amount of research. Rosehip extracts have a high concentration of flavonoides and polyphenols, which suggests that these compounds may have antioxidant properties [39]. These compounds have been shown to inhibit the migration and proliferation of cancer cells in the MCF-7, HT-29, and HeLa cell lines, respectively. Despite this, there has not been a sufficient amount of study conducted on the effectiveness of rosehip extracts and the bioactive components that they contain in preventing the development of generalised breast cancer cells [40].

It has been demonstrated beyond a reasonable doubt that the AKT and MAPK signalling pathways, in particular, favour the development of gliomas and other types of brain tumours. It has been established that genetic anomalies that enhance the epidermal growth factor receptor (EGFR), p53, and phosphatase and tensin homolog (PTEN) mutations are associated with alterations in the signalling pathways of AKT and MAPK in glioblastoma multiforme (GBM) [41]. It has been established that AKT signalling in GBMs is associated with an increase in cell proliferation, invasion, and angiogenesis, while at the same time decreasing apoptosis on the other hand. Silencing AKT with siRNA oligonucleotides is one method that can be utilised to inhibit the proliferation of GBM cells and simultaneously promote their demise [42]. The combination of reseveratrol and AKT silencing results in an increase in the mortality of GBM cells. In addition, the downregulation of PI3K, which is an upstream kinase for AKT, through the use of siRNA has been shown to significantly increase apoptosis and decrease the growth of GBM cells. There is evidence to show that the activation of the MAPK pathway by EGFR mutations or amplification speeds up the processes of cell proliferation, invasion, and migration observed in GBM cells. However, these research have neglected to particularly study the anti-tumor potential of rosehip extracts and have failed to define which signalling pathways are disrupted [43].

Rosa canina antioxidant activity

An evaluation of the radical scavenging activity of the methanolic *Rosa canina* L. extracts was carried out by determining whether or not they were able to neutralise DPPH radicals. Due to the fact that prior research discovered that total phenolics, rather than individual phenolic components, correlate better with the antioxidant activity of plant extracts, this study focused on the overall phenol content. Claudiosides, flavonols, antocyanidins, and stilbens are the four primary categories of phenols. The capacity of these phenols to scavenge free radicals differs according on the chemical structure of the phenols. Due to the fact that even within a certain group, individual compounds can have varied antioxidant capacities, it is reasonable to assume that the same quantities of phenolic compounds can elicit different antioxidant responses. In the case of RC5 (var. assiensis, Cluj, Manastur) and RC1 (var. transitoria f. ramosissima, BistritaNasaud, Agiesel), the antioxidant activity of the fruits of *Rosa canina* L. varied considerably, ranging from 63.35 µM Trolox/100 g sample to 127.8 µM Trolox/100 g sample. Cano and colleagues elaborated on the ABTS method, which was employed for the purpose of determining the overall antioxidant activity [44]. For the purpose of this experiment,

we made use of 2,2'-azino-bis-(3-ethylbenzoithiazolone-6-sulfonic acid), potassium persulfate, and the ABTS radical. A radical is formed after being exposed to darkness for sixteen hours. The calibration curve was obtained by adding 1500 µL of ABTS to the standard solution of ascorbic acid. Subsequently, the absorbance at 744 nm was measured in the UV spectra using a Jasco Spectrophotometer V-630 (Washington, USA). This analysis was performed in order to obtain the calibration curve. After swirling for one minute, the absorbance A, which is a representation of the signal that was suppressed, was measured. Following the preparation of a standard solution consisting of 4 millimolar ascorbic acid, the procedure was repeated while utilising six other ascorbic acid solutions with concentrations ranging from 90 to 300 micromolar. % Inhibition = 1-(A/A0) x 100 is the formula that may be used to determine the percentage of inhibition as a percentage. Following the collection of the calibration curve, the same procedure was utilised, which consisted of combining 25 microlitres of Rose sample with 1500 microlitres of ABTS. Milligrammes of ascorbic acid per gramme of dried fruit was the unit of measurement that was utilised to express the overall antioxidant activity [45].

Rosa canina anti-inflammatory activity

Forouzanfar et al.,2023 Since ancient times, people have been aware of the medicinal properties of the Nastaran plant, which is also classified as *Rosa canina*. In the current investigation, human umbilical vein endothelial cells (HUVECs) were used to evaluate the possible protective advantages of *R. canina* fruit extract (RCFE) and quercetin, a flavonoid component, against cell injury produced by hydrogen peroxide. Specifically, the researchers wanted to determine whether or not these properties could be beneficial. The Alamar Blue assay was utilised to study the protective effect on HUVEC cells. This was done after RCFE (1.25-20 µg/mL) and quercetin (1.25-20 µM) were subjected to H2O2-oxidizing agents (1 and 2 mM). In order to determine the amount of reactive oxygen species (ROS) that were present within the cell, we employed a fluorimetric method that included the DCFDA reagent. Flow cytometry and hypotonic PI labelling were utilised in this investigation to investigate the impact that RCFE and quercetin have on the process of cell death [46]. In order to determine the amounts of PARP and survivin, two proteins that have been linked to the process of cell death, we utilised western blotting. Through the use of the Alamar Blue test, it was revealed that quercetin and RCFE reduced the toxicity of H2O2. The survival of cells was significantly increased by RCFE and quercetin when they were tested against H2O2. Furthermore, it was found that quercetin and RCFE were able to prevent the production of reactive oxygen species (ROS) by H2O2. Following exposure of cells to hydrogen peroxide, it was shown that RCFE and quercetin exhibited a reduction in the apoptosis and sub-G1 peak region in the flow histogram [47].

Shakibaei et al.,2012 In order to investigate the biological effects of the botanical extracts, the chondrocytes were subjected to IL-1β for a duration of up to 72 hours. The expression of a number of proteins, such as collagen type II, cartilage-specific proteoglycan (CSPG), β1-integrin, SOX-9, COX-2, MMP-9, and MMP-13, was evaluated by the utilisation of Western blotting. The final word. In order to inhibit the activation of NF-κB that was caused by IL-1β, the botanical extracts were able to decrease the phosphorylation of p65, the degradation of IκBα, and the nuclear translocation of p65. There was a correlation between these events and the downregulation of NF-κB targets, which included COX-2 and MMPs. In a similar manner, the extracts were able to reverse the downregulation of collagen type II, CSPG, β1-integrin, and cartilage-specific transcription factor SOX-9 protein expression that was brought about by IL-1β. Although the presence of IL-1β was present, the presence of botanical extracts in high-density cultures continued to promote the creation of new cartilage. Through the utilisation of botanical extracts, it was demonstrated that chondrocytes were able to experience both anti-inflammatory and anabolic benefits. In light of the fact that IL-1β-induced NF-κB activation was discovered to be diminished, it is imperative that further study be conducted in order to demonstrate that plant extracts possess potential in the treatment of osteoarthritis (OA) and other diseases where NF-κB plays a role in pathophysiology [48].

Lattanzio et al. The *Rosa canina* L. shrub, which is used for medicinal purposes, is utilised extensively in traditional folk medicine. Several chemicals that were produced from rose hip extracts were found to possess anti-inflammatory effects based on in vitro testing. In order to examine the extract's potential anti-inflammatory effects, the carrageenin-induced rat paw oedema experimental model was utilised. An damage model of the stomach that was produced by ethanol was utilised in order to investigate the gastroprotective effect. Quantification of the in vitro antioxidant activity of this extract was also accomplished by the use of the Total Phenolic Content, the Trolox Equivalent Antioxidant Capacity approach, and the Briggs-Rauscher oscillating reaction. The research findings indicate that the Rosa canina extract possesses anti-inflammatory characteristics that are comparable to those of indomethacin and that it inhibits the formation of oedema that is caused by carrageenin. A greater quantity of the extract was required to induce an antiedema effect that was more prominent. In spite of the fact that there was no statistically significant antiulcerogenic efficacy, the overall score that indicated gastric damage was lower in stomachs that had been pre-treated with *Rosa canina* in comparison to stomachs that had not been treated. In spite of the fact that the total score indicating gastrointestinal injury was lower in Rosa canina stomachs from pre-treated rats in comparison to those from untreated rats, the antiulcerogenic effects were not statistically detectable. According to the findings of scientific tests, the extract's powerful antioxidant activity may be responsible, at least in part, for its anti-inflammatory functions in living organisms [49].

Winther et al. Since more than two thousand years ago, herbalists have been making use of *Rosa canina* pseudo fruits, which are sometimes referred to as rose hips. However, scientists have only just begun to identify the specific mechanisms by which this plant product positively impacts human health. Fatty acids (FAs), flavonoids, and carotenoids are only some of the many compounds that have been found, and the bioactivity of these chemicals has been the topic of speculation ever since they were discovered. A significant amount of study has been conducted on flavonoids, which have been found to have more than 4,500 different representations. The findings of this research suggest that various structures within flavonoids may be

chemicals that are beneficial to health, and this is also the case with rose hips. The importance of *R. canina* carotenoids is currently being debated as a result of the absence of compelling evidence of specific bioactivity among this group. The FAs that are helpful to human health have been identified over decades of research, and some of these FAs are even regarded "essential" for human species to continue existing. With the help of research, the precise bioactivity processes that are linked to three FAs that are found in abundance in *R. canina* fruits have been brought to light. As an example, let us take into consideration linoleic acid, α-linolenic acid (which is largely discovered in the seeds of *R. canina*), and a galactolipid ((2S)-1,2-di-O-[(9Z,12Z,15Z)]).The compound known as 3-O-β-D-galactopyranosyl glycerol, also known as octadeca-9-12-15-trienoylGOPO, is recognised for its ability to exhibit anti-inflammatory properties [50].

CONCLUSION

The rich bioactive components that may be found in rosehips and their by-products, including as polyphenols, carotenoids, vitamins, tocopherols, vital fats, and minerals, have recently garnered a lot of attention due to the possible health benefits that they may offer. These compounds have been linked to a wide variety of beneficial effects, including anti-inflammatory, antioxidant, anticancer, and hepatoprotective properties, amongst others. Despite the fact that rosehips have positive impacts on health, there has been a lack of research conducted on the bioactive components of rosehips and the potential applications of rosehips in functional products. The rich bioactive components that may be found in rosehips and their by-products, including as polyphenols, carotenoids, vitamins, tocopherols, vital fats, and minerals, have recently garnered a lot of attention due to the possible health benefits that they may offer. These compounds have been linked to a wide variety of beneficial effects, including anti-inflammatory, antioxidant, anticancer, and hepatoprotective properties, amongst others. Despite the fact that rosehips have positive impacts on health, there has been a lack of research conducted on the bioactive components of rosehips and the potential applications of rosehips in functional products. Variability in growing circumstances, harvest timings, and processing techniques all contribute to the presence of bioactive chemical variability in concentration and composition, which in turn has an effect on the consistency and effectiveness of the product. In addition, in order to evaluate the bioactivity of these substances in a variety of settings and for research purposes, standards are required. Due to the high cost and technical complexity of using advanced extraction and formulation procedures, it is possible that products made from rosehips will not be commercially viable or scalable. Last but not least, there are regulatory hurdles to overcome, such as the necessity of conducting exhaustive safety and effectiveness testing prior to the sale of the product on the market.

REFERENCES

1. Zhou Y, Hong Y, Huang H. Triptolide attenuates inflammatory response in membranous glomerulo-nephritis rat via downregulation of NF-κB signaling pathway. Kidney and Blood Pressure Research. 2016 Dec 23;41(6):901-10.
2. Medzhitov R. Inflammation 2010: new adventures of an old flame. Cell. 2010 Mar 19;140(6):771-6.
3. Chen L, Deng H, Cui H, Fang J, Zuo Z, Deng J, Li Y, Wang X, Zhao L. Inflammatory responses and inflammation-associated diseases in organs. Oncotarget. 2017 Dec 14;9(6):7204.
4. Chertov O, Yang D, Howard OM, Oppenheim JJ. Leukocyte granule proteins mobilize innate host defenses and adaptive immune responses. Immunological reviews. 2000 Oct 1;177:68-78.
5. Jabbour HN, Sales KJ, Catalano RD, Norman JE. Inflammatory pathways in female reproductive health and disease. Reproduction. 2009 Dec 1;138(6):903.
6. Guo Q, Jin Y, Chen X, Ye X, Shen X, Lin M, Zeng C, Zhou T, Zhang J. NF-κB in biology and targeted therapy: new insights and translational implications. Signal Transduction and Targeted Therapy. 2024 Mar 4;9(1):53.
7. Yu H, Lin L, Zhang Z, Zhang H, Hu H. Targeting NF-κB pathway for the therapy of diseases: mechanism and clinical study. Signal transduction and targeted therapy. 2020 Sep 21;5(1):209.
8. Shih RH, Wang CY, Yang CM. NF-kappaB signaling pathways in neurological inflammation: a mini review. Frontiers in molecular neuroscience. 2015 Dec 18;8:77.
9. Xiao K, Liu C, Tu Z, Xu Q, Chen S, Zhang Y, Wang X, Zhang J, Hu CA, Liu Y. Activation of the NF-κB and MAPK Signaling Pathways Contributes to the Inflammatory Responses, but Not Cell Injury, in IPEC-1 Cells Challenged with Hydrogen Peroxide. Oxidative Medicine and Cellular Longevity. 2020;2020(1):5803639.
10. Ebrahimi N, Abdulwahid AH, Mansouri A, Karimi N, Bostani RJ, Beiranvand S, Adelian S, Khorram R, Vafadar R, Hamblin MR, Aref AR. Targeting the NF-κB pathway as a potential regulator of immune checkpoints in cancer immunotherapy. Cellular and Molecular Life Sciences. 2024 Dec;81(1):106.
11. Awuchi CG, Amagwula IO, Priya P, Kumar R, Yezdani U, Khan MG. Aflatoxins in foods and feeds: A review on health implications, detection, and control. Bull. Environ. Pharmacol. Life Sci. 2020 Aug 9;9:149-55.
12. Saha P, Kumar A, Bhanja J, Shaik R, Kawale AL, Kumar R. A review of immune blockade safety and antitumor activity of dostarlimab therapy in endometrial cancer. International Journal for Research in Applied Sciences and Biotechnology. 2022 Jun 22;9(3):201-9.
13. Chen L, Wang J, Ren Y, Ma Y, Liu J, Jiang H, Liu C. Artesunate improves glucose and lipid metabolism in db/db mice by regulating the metabolic profile and the MAPK/PI3K/Akt signalling pathway. Phytomedicine. 2024 Apr 1;126:155382.
14. Saleem S. Targeting MAPK signaling: A promising approach for treating inflammatory lung disease. Pathology-Research and Practice. 2024 Jan 11:155122.
15. Shi A, Liu L, Li S, Qi B. Natural products targeting the MAPK-signaling pathway in cancer: overview. Journal of Cancer Research and Clinical Oncology. 2024 Jan;150(1):6.
16. Roman I, Stănilă A, Stănilă S. Bioactive compounds and antioxidant activity of Rosa canina L. biotypes from spontaneous flora of Transylvania. Chemistry central journal. 2013 Dec;7:1-0.
17. Wanes D, Jabri MA, Tounsi H, Rtibi K, Zouari N, Hajji N, Jridi M, Abdellaoui A, Sebai H. Chemical characterization of bioactive components of Rosa canina extract and its protective effect on dextran sulfate sodium-induced intestinal bowel disease in a mouse model. Journal of medicinal food. 2020 Oct 1;23(10):1109-19.
18. Negrean OR, Farcas AC, Nemes SA, Cic DE, Socaci SA. Recent advances and insights into the bioactive properties and applications of Rosa canina L. and its by-products. Heliyon. 2024 May 7.
19. Lawrence T. The nuclear factor NF-κB pathway in inflammation. Cold Spring Harbor perspectives in biology. 2009 Dec 1;1(6):a001651.
20. Shih RH, Wang CY, Yang CM. NF-kappaB signaling pathways in neurological inflammation: a mini review. Frontiers in molecular neuroscience. 2015 Dec 18;8:77.
21. Oeckinghaus A, Ghosh S. The NF-κB family of transcription factors and its regulation. Cold Spring Harbor perspectives in biology. 2009 Oct 1;1(4):a000034.

22. Liu T, Zhang L, Joo D, Sun SC. NF-κB signaling in inflammation. Signal transduction and targeted therapy. 2017 Jul 14;2(1):1-9.

23. Zhang T, Ma C, Zhang Z, Zhang H, Hu H. NF-κB signaling in inflammation and cancer. MedComm. 2021 Dec;2(4):618-53.

24. Wang S, Liu Z, Wang L, Zhang X. NF-κB signaling pathway, inflammation and colorectal cancer. Cellular & molecular immunology. 2009 Oct;6(5):327-34.

25. Salminen A, Hyttinen JM, Kaarniranta K. AMP-activated protein kinase inhibits NF-κB signaling and inflammation: impact on healthspan and lifespan. Journal of molecular medicine. 2011 Jul;89:667-76.

26. Saha P, Kumar R, Nyarko RO, Kahwa I, Owusu P. Herbal Secondary Metabolite For Gastro-Protective Ulcer Activity With Api Structures.

27. Roberti A, Chaffey LE, Greaves DR. NF-κB signaling and inflammation—Drug repurposing to treat inflammatory disorders?. Biology. 2022 Feb 26;11(3):372.

28. O'Dea E, Hoffmann A. NF-κB signaling. Wiley Interdisciplinary Reviews: Systems Biology and Medicine. 2009 Jul;1(1):107-15.

29. Napetschnig J, Wu H. Molecular basis of NF-κB signaling. Annual review of biophysics. 2013 May 6;42(1):443-68.

30. Bhat AA, Afzal O, Agrawal N, Thapa R, Almalki WH, Kazmi I, Alzarea SI, Altamimi AS, Kukreti N, Chakraborty A, Singh SK. A comprehensive review on the emerging role of long non-coding RNAs in the regulation of NF-κB signaling in inflammatory lung diseases. International journal of biological macromolecules. 2023 Sep 19:126951.

31. Kim EK, Choi EJ. Pathological roles of MAPK signaling pathways in human diseases. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease. 2010 Apr 1;1802(4):396-405.

32. Yue J, López JM. Understanding MAPK signaling pathways in apoptosis. International journal of molecular sciences. 2020 Mar 28;21(7):2346.

33. Zhang W, Liu HT. MAPK signal pathways in the regulation of cell proliferation in mammalian cells. Cell research. 2002 Mar;12(1):9-18.

34. Geest CR, Coffer PJ. MAPK signaling pathways in the regulation of hematopoiesis. Journal of leukocyte biology. 2009 Aug;86(2):237-50.

35. Keren A, Tamir Y, Bengal E. The p38 MAPK signaling pathway: a major regulator of skeletal muscle development. Molecular and cellular endocrinology. 2006 Jun 27;252(1-2):224-30.

36. Braicu C, Buse M, Busuioc C, Drula R, Gulei D, Raduly L, Rusu A, Irimie A, Atanasov AG, Slaby O, Ionescu C. A comprehensive review on MAPK: a promising therapeutic target in cancer. Cancers. 2019 Oct 22;11(10):1618.

37. Bahar ME, Kim HJ, Kim DR. Targeting the RAS/RAF/MAPK pathway for cancer therapy: from mechanism to clinical studies. Signal transduction and targeted therapy. 2023 Dec 18;8(1):455.

38. Cheng Y, Chen J, Shi Y, Fang X, Tang Z. MAPK signaling pathway in oral squamous cell carcinoma: biological function and targeted therapy. Cancers. 2022 Sep 23;14(19):4625.

39. García-Hernández L, García-Ortega MB, Ruiz-Alcalá G, Carrillo E, Marchal JA, García MÁ. The p38 MAPK components and modulators as biomarkers and molecular targets in cancer. International journal of molecular sciences. 2021 Dec 29;23(1):370.

40. Yuan W, Shi Y, Dai S, Deng M, Zhu K, Xu Y, Chen Z, Xu Z, Zhang T, Liang S. The role of MAPK pathway in gastric cancer: unveiling molecular crosstalk and therapeutic prospects. Journal of Translational Medicine. 2024 Dec 24;22(1):1142.

41. Wei J, Liu R, Hu X, Liang T, Zhou Z, Huang Z. MAPK signaling pathway-targeted marine compounds in cancer therapy. Journal of Cancer Research and Clinical Oncology. 2021 Jan;147:3-22.

42. Arafa ES, Refaey MS, Abd El-Ghafar OA, Hassanein EH, Sayed AM. The promising therapeutic potentials of ginsenosides mediated through p38 MAPK signaling inhibition. Heliyon. 2021 Nov 1;7(11).

43. Yan Y, Dai T, Guo M, Zhao X, Chen C, Zhou Y, Qin M, Xu L, Zhao J. A review of non-classical MAPK family member, MAPK4: A pivotal player in cancer development and therapeutic intervention. International Journal of Biological Macromolecules. 2024 May 25:132686.

44. Shi A, Liu L, Li S, Qi B. Natural products targeting the MAPK-signaling pathway in cancer: overview. Journal of Cancer Research and Clinical Oncology. 2024 Jan;150(1):6.

45. Chen RE, Thorner J. Function and regulation in MAPK signaling pathways: lessons learned from the yeast Saccharomyces cerevisiae. Biochimica et Biophysica Acta (BBA)-Molecular Cell Research. 2007 Aug 1;1773(8):1311-40.

46. Zhang W, Liu HT. MAPK signal pathways in the regulation of cell proliferation in mammalian cells. Cell research. 2002 Mar;12(1):9-18.

47. Jiménez S, Gascón S, Luquin A, Laguna M, Ancin-Azpilicueta C, Rodríguez-Yoldi MJ. Rosa canina extracts have antiproliferative and antioxidant effects on Caco-2 human colon cancer. PloS one. 2016 Jul 28;11(7):e0159136.

48. Roman I, Stănilă A, Stănilă S. Bioactive compounds and antioxidant activity of Rosa canina L. biotypes from spontaneous flora of Transylvania. Chemistry central journal. 2013 Dec;7:1-0.

49. Forouzanfar F, Tabatabaei Z, Emami SA, Ayati Z, Tayarani-Najaran Z. Protective effects of fruit extract of Rosa canina and quercetin on human umbilical vein endothelial cell injury induced by hydrogen peroxide. Food Science & Nutrition. 2023 Dec;11(12):7618-25.

50. Khelfi S, Zerizer S, Bensouici C, Tebibel S, Kabouche Z. The antioxidant activity and the protective effect of Rosa canina L. fruit against intestinal inflammation induced by hyperhomocysteinemia in mice. Pharmaceutical Chemistry Journal. 2024 Feb;57(11):1778-88.

51. Shakibaei M, Allaway D, Nebrich S, Mobasheri A. Botanical extracts from Rosehip (Rosa canina), Willow Bark (Salix alba), and Nettle Leaf (Urtica dioica) suppress IL-1β-induced NF-κB activation in canine articular chondrocytes. Evidence-Based Complementary and Alternative Medicine. 2012;2012(1):509383.

52. Lattanzio F, Greco E, Carretta D, Cervellati R, Govoni P, Speroni E. In vivo anti-inflammatory effect of Rosa canina L. extract. Journal of ethnopharmacology. 2011 Sep 1;137(1):880-5.

53. Winther K, Sophie Vinther Hansen A, Campbell-Tofte J. Bioactive ingredients of rose hips (Rosa canina L) with special reference to antioxidative and anti-inflammatory properties: in vitro studies. Botanics: Targets and Therapy. 2016 Feb 29:11-23.