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A Review of the Effect of Plant-derived Bioactive Substances on the Inflammatory Response of Ruminants (Sheep, Cattle, and Goats)

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Abstract

Inflammation is a complex but defensive biological response of living tissue to infection that can be triggered by exogenous injury and infectious agents such as bacteria and viruses. Inflammation is part of the innate immune response acting as the first line of defense against pathogens and disease. The inflammatory response acts as a double-edged sword because if inflammation persists or augments, it may switch from a defensive mechanism to a detrimental process, therefore, modulating the inflammatory response using therapeutic interventions is important for animal health and well being and for long-term food security. Recent studies have reported that plant-derived bioactive compounds are precursors for numerous anti-microbial and anti-parasitic medicines. The antibiotic activities may be attributed to some bioactive compounds such as polyphenols, flavonoids, terpenes, tannins, terpenoids, vitamin C, essential oils, and carotenoids. The ban on the use of synthetic antibiotics and inconsistent efficacy of non-steroidal anti-inflammatory drugs as NSAID have elevated the need for alternative drugs, particularly, those which are derived from plant-based bioactive compounds. Such substances can be used as supplements in animal food to boost the immune system particularly, for domestic ruminants, which are the main source for milk and meat for humans. During the past recent years, plant-based bioactive substances were studied intensively along with their anti-inflammatory and other therapeutic effects, both *in-vivo* and *in-vitro*. Modulating the inflammatory response using plant-based bioactive compounds is important for understanding the anti-inflammatory pathways that stimulate the innate immune response to pathogens or injury. The present study is a literature review that focuses on the applications of plant-derived bioactive substances and their effects on the immune responses of goats, sheep, and cows.

Keywords

Inflammation; Ruminants; Innate immunity; Cytokines; Plant bioactive compounds

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Inflammation and the Innate Immune Response

Ruminants are a group of mammals characterized by having four-chambered stomachs. To obtain nutrients from plant-based food, they can ferment them in a specialized chamber called rumen through microbial actions aiding in digestion. Cattle, sheep and goats which are the three ruminants globally consumed as sources of animal protein, contribute substantially to the economy. Inflammatory diseases cause significant losses to the livestock industry with public health and economic consequences.

There is a close nexus between healthy animals, innate immunity, and the inflammatory response. Since inflammation is the harbinger of upcoming disease, addressing the cause of inflammation and modulating it is essential for animal health and productivity. Inflammation is a complex but defensive biological response of living tissue to infection triggered by exogenous injury and baleful stimuli due to pathogens [1]. The innate immune system is the first line of a host defense mechanism that is responsible for the fast pathogen recognition and activation of the pro-inflammatory response. The effective immune response requires proper crosstalk between pro- and anti-inflammatory cytokines because their strong interaction not only governs local inflammatory reactions but also generates systemic effects through blood circulation [2]. Being a vital part of both innate and acquired immunity, inflammation orchestrates the body's immune system responses through leukocytes, chemokines, and cytokines signaling to reconcile homeostasis. Pattern recognition receptors (PRR) such as Toll-like receptors (TLRs) are the ones that sense the invading microbes or traumatized cells and activate the local and systemic immune response that, in turn, stimulates four cardinal signs of inflammation which are redness, hotness, swelling & pain in the affected area.The redness of tissues is caused by the momentary vasoconstriction due to the injury following by vasodilatation to facilitate the infiltration of more fluids, cytokines, macrophages, and proteins to the affected area, heat results from enhanced blood flow, swelling, and pain. The heat is raised in the injured area due to the increased blood flow, while tissue swelling is due to the leaking of fluid from blood vessels to the affected tissue, consequently swelling causes pain due to the sensation and stimulation of the nerves in the area [3,4]. In particular, invasion of pathogenic microbes incites an intricate process that promotes the production and release of pro-inflammatory cytokines, which are hormone-like polypeptides such as tumor necrosis factor (TNF-α), interferons (IFN-γ), and interleukins (IL-6) [5]. The augmented level of pro-inflammatory cytokines in blood evokes a number of systemic changes in the body such as fever, reduced appetite, gastric function, plasma iron, and zinc levels, which stimulate the activity of lymphocytes and neutrophils with subsequent phagocyte mobilization and acute-phase proteins, altered metabolism of carbohydrates, lipids and proteins cumulatively called as acute phase response (APR) [2]. Activated mononuclear cells release monocytes and macrophages that primarily synthesize TNF-α, and IL-1β to act against bacterial pathogens while in the case of viral infection, IFN-γ is released from T-cells. Sustained inflammation is associated with oxidative damage due to the release of radicals by leukocytes and can result in deleterious effects on the host. Interlinked signaling events in cells and their consequences result in symptoms of inflammation that cannot be overlooked because if the condition of inflammation persists or augments, it may switch from a defensive mechanism to a detrimental process [3].

Inflammation and the Acute Phase Response (APR)

Infection and injury may result in an APR initiated primarily by tissue macrophages or blood monocytes. Pro-inflammatory cytokines may trigger the production of acute-phase proteins in the liver and their release in the blood in an effort to neutralize any pathological change, which may trigger the acute inflammation signs. For example, pro-inflammatory cytokines TNF-α, IL-6, and IL-1 can counteract endotoxin and restore homeostasis [6]. In response to cytokines, several signal cascades are propagated, causing cortisol secretion and, eventually the release of some acute-phase proteins such as serum amyloid A (SAA), C-reactive proteins, fibrinogen and haptoglobin by the liver. C-reactive protein and SAA are used in medical laboratories to identify tissue injury and the stage of inflammation, which helps in the prognosis and determination of treatment options [7]. The APR is crucial in regulating defense mechanisms including initiation of the defense process, immune cell production, metabolic changes, and fever to combat pathogens [8].

Types of Inflammation

Inflammation can be categorized into acute and chronic inflammation depending on its severity and the nature of injury and pathogen causing the inflammation. Acute inflammations are prominent and rapid mainly governed by neutrophils and may cause injury to the tissues. On the other hand, chronic inflammation can cause severe injury to the tissues and is often mediated by lymphocytes, monocytes/ macrophages and may involve neutrophils. The onset of chronic inflammation is indeed a gradual process over a protracted period;thus, the symptoms are less conspicuous [7].

Inflammation and immune activation in ruminants

Cattle, sheep, and goats are domestic animals providing the human with meat and dairy products that are rich in proteins. The ruminants adapted to feed on varieties of plants, particularly in open grazing fields, which make them vulnerable to numerous bacterial, viral, and parasitic diseases. Their exposures to such pathogenic microbes and other factors will make those ruminants prone to some infectious disease and parasitic infestation that may induce inflammation as defense counter-reaction to minimize or neutralize the damage created by the introducing pathogens. The inflammatory response to foreign agents results from a series of signaling pathways the formation of antibodies and other defense mechanisms as a part of the immune response. Pathogen associated molecular patterns (PAMPS) can be modulated by plants based bioactives [9]. The recognition of PAMPS by pathogen recognition receptors (PRR) is central to understanding the innate immune response and the design of plant-based modulators of inflammation [10].

In domestic ruminants, *E. coli* is the major cause of mastitis, which impacts greatly on milk production, and neutrophils play a central role in the inflammatory response associated with *E. coli* mediated mastitis **[**10,11**]**. In particular**,** TLRs upon binding with LPS, a major inflammatory inducerstimulates innate immunity responses, and this process is accompanied by LPS-binding proteins (LBP) and a cluster of differentiation antigen 14 (CD14) [12]. TLRs recognize a variety of conspicuous microbial patterns including LPS, flagellin, viral RNA (double-stranded), and CpG (unmethylated) motifs [13]. Besides immune and inflammatory responses, cell proliferation and differentiation invariably depend on the transcription of nuclear factor κB (NF-κB) which is found to be inactive in cell cytoplasm with its inhibitory κB (IκB) counterparts. The NF-κB signaling pathway is being triggered by LPS and various receptors such as TLRs, tumor necrosis factor receptor (TNF-R), and interleukin 1 receptor (IL-1R), which in turn initiates phosphorylation of inactive NF-κB-I-κB. Later, activated NF-κB is released, enters the nucleus, and binds with its promoter to upregulate the transcription of proinflammatory cytokines including interleukin 1-beta (IL-1β), IL-6, IL-8, and hormone-like polypeptide tumor necrosis factor-alpha (TNF-α) [14]. Several pieces of research articles also supported the implication of LPS in the propagation of inflammatory responses.

Demonstrated that bacterial pathogens like *M. haemolytica* infected cattle [15] demonstrated high levels of tumor necrosis factor-alpha (TNF-α), interleukin 1-beta (IL-1β), and interferon-γ (IFN-γ), [16] also reported a rising level of TNF-α, IL-1β, and IFN-γ upon LPS intravenous administration. In lactating dairy cows, [13] showed that digestive tract derived LPS stimulates inflammatory gene expression and obstructs casein synthesis.

Infection by viral pathogens activatescytokine gene expression. Cattle infected with the bovine respiratory syncytial virus (BRSV) showed high IL-6 and IFN-γ levels while infection with bovine viral diarrhea virus (BVDV) raised levels of TNF-α, IL-1β, as well as IL-6 [17]. However, cattle infected with both viral and bacterial infection demonstrated noticeably increased TNF-α, IL-6, IFN-γ except IL-1β [15]. Variation in innate immunity has been observed [18]. The TLR and cytokine responses of susceptible and resistant varieties of goats and water buffalo to *pestes des petits* ruminant virus (PPRV) was observed differently. Naturally, PPRV susceptible goats showed a weak immune response with high viral loads and poor TLRs expression. On the other hand PPRV resistant breeds, where synthetic TLRs agonists mediated peripheral blood mononuclear cells stimulation showed a remarkably higher level of pro-inflammatory cytokines including IFN- γ with the mitigated expression of immunosuppressive cytokine IL-10. The difference in immune response was attributed to higher IFN- γ and TLR-7 response in resistant variety that restricted PPRV replication.

Disease

It has been reported yearly that the diseases affected ruminants have a huge economic impact globally as well as the impact on human health. The bacterial mastitis is one of the chief culprits of economic losses in the dairy industry. Upon mastitis, bacteria invade the epithelial tissue of the mammary gland causing the death of some cells by necrosis. The bacterial invasion causes the inflammation to mobilize the white blood cells and neutrophils, which attack the bacteria, ingests them and release soluble anti-microbials to neutralize the infection and its impact on the mammary gland [19].

Long-term intake of grain-enriched diets by ruminants leads to subacute ruminal acidosis (SARA) which may cause a number of malfunctions including increased intestinal permeability, alteration in microflora, metabolic disorders, lowering of ruminal pH to 5.8, reduction of cellulolytic bacteria with subsequent increase in starch-fermenting and lactic acid-producing bacteria [20]. It has been reported that low pH in rumen causes the lysis of gram-negative bacteria, and the effect of acidosis on the free ruminal lipopolysaccharides content (LPS) is strong evidence of inflammation [21]. After the onset of local inflammation in the ruminal epithelium, LPS passes through epithelial barrier reaching into the blood, and there it causes systemic inflammation by activating pro-inflammatory cytokines such as tumor necrosis factor (TNF)-α, interleukin IL-1β and IL-6. The release of IL-8 release further deploys various adaptor molecules leading to the transcriptional factor activation of NF-κB [22,23]. The initiation of inflammatory signals simultaneously affectsbody tissues in terms of energy and lipid metabolism.

Also, systemic inflammation at organ level increases acute phase proteins secretion (serum amyloid A, haptoglobin), fever, elevated cortisol level. The crucial role of serum amyloid A is to bind endotoxin and nullify its effect in the blood, whereas haptoglobin binds with free plasma hemoglobin, thereby preventing iron availability to bacteria required for their growth and multiplication. The most prominent consequences of SARA are the malfunctioning of the cellular junction and cellular adhesion that leads to redundant infiltration of pathogens/toxins into blood from the lumen. However, systemic inflammation is a defensive mechanism to restore homeostasis, although inflammation for a protracted period can disrupt energy and lipid metabolism, immune inhibition, and disease susceptibility [6].

Inflammation and reproduction physiology

In ruminants, inflammation has been an inevitable part of reproductive physiology. In many cases, it acts as a limiting factor because of its nexus to the chemokines and cytokines activation, infiltration of immune cells and blood vessel dilation. The female genital organs experience inflammation when subjected to endometritis, ovulation, luteolysis, corpus luteum development, intrauterine microbial encounters, post insemination uterine clearance, placental expulsion, or post-partum [3]. Therefore, to combat pathogens and tissue injury, the female genital tract has receptors in the form of pattern recognition receptors (PRR), microbe-associated molecular patterns (MAMPs), and damage-associated molecular patterns (DAMPs). These receptors can identify either highly specific microbial signatures or cell damage.

The most common PRR are TLRs that are located in different bovine granulosa cells, oviductal epithelial cells, and epithelial and stromal cells of the endometrium [24]. Upon recognition of MAMPs or DAMPs by the receptors on the abovementioned cells starts gushes of signaling events (NF-κB or MAPkinase) that, in turn, activates pro-inflammatory mediators (IL-1, IL-8, TNF-α). As a result, it leads to vasodilation, tissue healing, reactive oxygen species generation, and infiltration of macrophage and neutrophil to aid phagocytosis. Besides, several metabolites, peptides with antimicrobial properties,and apoptosis suppressing factors have also be released [3,25,26].

Metabolic disorders

Due to metabolic changes, the immune function of transition cows gets suppressed and consequently unable to regulate inflammation. Thus the animals are repeatedly in a pro-inflammatory stage without any known causes [3]. Recent studies indicated that acute inflammatory conditions and the presence of endotoxin might be implicated inthe displaced abomasum, liver triglyceride accumulation, liver abscesses, lipolysis, laminitis, mineral fluctuation, and downer cow syndrome [6,27].

To ascertain the exact reason, the studies which were conducted with mastectomized cows have found that neither gestation nor calving was responsible for the prolonged pro-inflammatory stage. However, it was found that lactation and metabolic changes during the transition period were the real culprits [28]. The studies have also shown that there is a close nexus between metabolic disorders and the responsiveness of immune cells. The skewed dietary shifts in transition cows may also lead to systemic inflammation. Moreover, during the transition period, monocytes are noticed to be highly receptive to inflammatory stimulants, which in turn provoke more production of inflammatory cytokines, which is followed by systemic inflammation and altered liver metabolism. The elevated ketone levels in blood, hypocalcemia, and non-esterified fatty acid concentration greatly affect the immune cells to the pathogenic signals which result in mitigated immune function.

Ectoparasites and endoparasite

In ruminants, both endoparasites for examples gastrointestinal nematodes and trematodes [29] and ectoparasites [30] such as chewing/biting lice pose a great threat to the health of farm animals and their heavy infestation is one of the leading causes of death loss in ruminants, which tremendously affects the costs production losses to the livestock industry. Although nematodes such as *Haemonchus contortus, Trichostrongylus colubriformis, Ostertagia ostertagi, Teladorsagia circumcincta*, and trematodes such as *Fasciola hepatica* or ectoparasites include a wide variety of species that causes the infestation, the mode of the ruminant immune response is similar for all parasites. It has been reported that these invasive parasites lead a sponging lifestyle in the host organism by inducing Th2 immunity, and there is a positive correlation between Th2 response and parasitic load [31]. The parasite driven Th2 immune activation also engages IL-4, IL-5, IL-13, immunoglobin E (IgE), mast cells, eosinophils, and basophils. Being more skewed towards Th2 immunity, parasites can inhibit protective, pro-inflammatory Th1 immunity response to invade cytotoxic effect of the host immune system. Moreover, this strategy enables parasites to regulate the immune system, penetration into the intestinal wall with downregulation of parasite-driven IL-4 synthesis and upregulation of IL-10 and TGF-β production [29]. In ectoparasitic diseases, the acuteness of inflammatory skin lesions primarily depends on the balance between (Th1/Th2) cytokine response, the extent of the inflammation, and reactive oxygen species and can cause severe hypersensitivity [32].

Inflammation and Oxidative Stress

Several pieces of evidencehave shownthe implication of lipid peroxides in inflammation. Upon exposure toreactive oxygen species (ROS) including hydrogen peroxides, intracellular lipids form lipid peroxides [33]. During early lactation, non-esterified fatty acid (NEFA) is produced by adipose tissues in a high amount. To tackle high NEFA and maintaining body lipid homeostasis, liver augments peroxisomal oxidation, which is an alternate route for fatty acid oxidation and then that process may end up with excessive hydrogen peroxide production. These peroxides stimulate systemic inflammatory cascades, thereby impairing the immune cell's responsiveness to infection and maladaptive shifts in metabolism [34].

Current Anti-Inflammatory Treatments

The continuous use of antibiotics has been practicing for the treatment of LPS induced mastitis that reflects putative risks of antibiotic resistance and their potential residues in milk that eventually goes to human through the food chain [35]. After the ban on several antibiotics, the use of non-steroidal anti-inflammatory (NSAID) has emerged as an alternative treatment, but they were found not very promising. To treat early lactation inflammation, acommercial NSAID drug sodium salicylate was used on 78 cows including control for the first seven days of lactation [36]. With average outcome at the beginning, the oldest cohort treated with salicylate yielded 21% more milk over the whole lactation and 30% more milk fat than parity matched control as lactation progressed. However, salicylate treatment outcome in primiparous cows was not promising because of low milk yield that might be attributed to the difference in response to inflammatory signals or baseline inflammatory status [37,38]. The whole-lactation productivity of multiparous cows was ascertained on 153 cows. Cows were assigned to postpartum treatment with two drugs, one with sodium salicylate forthree days and second with meloxicam for one day compared to the control group [38]. Despite the short treatment duration of the drug, there was a fruitful effect of either salicylate or meloxicam on milk production (10% hike) compared to control. Butyrate (volatile fatty acids) and its salts (sodium butyrate) have been claimed to diminish inflammatory responses by reducing the NF-κB signaling pathwayand LPS mediated cytokine expression. In dairy goats, sodium butyrate administration improves inflammation, which was caused by a high concentrate fed diet by downregulation of pro-inflammatory cytokines (IL-6, IL-1β, TNF-α) in rumen epithelium [39]. These results witnesses that the effect of NSAID has not been consistent.

Immunomodulation

In the past few years, immunomodulation has emerged as a novel approach to combat inflammation and enhance the immune function of desired attributes in animals. Neutrophils, which are the most abundant leukocytes, are an integral part of the innate immune system containing cytoplasmic granules, glycogen, and polymorphic segmented nucleus [40]. Neutrophils are the first line of defense at the infection site as they bear several receptors on its surface, which can sense chemo-attractants (IL-8) secreted through tissue macrophage. The binding/interactionof neutrophils and chemo-attractants activates the optimum bactericidal activity of neutrophil that prompts their migration to the site of infection. Also, two superior attributes of neutrophils, such as ROS production (superoxide) and firm adhesion to endothelium, are central in pathogen killing [41]. Thus, targeting neutrophils with specific immunomodulatory molecules is apt for anti-inflammatory and antioxidant therapies.

Genetics contributes substantially to an animal's innate immunity by plant bioactive substances and modulate gene expression through activating the innate and adaptive immune response. It can underpin alternate control strategies to target gene-specific modulation to curb inflammation either by stimulating inflammation so that there is rapid pathogen elimination or can dampen inflammation to reduce oxidative damage. Galectins, (gal) carbohydrate-binding proteins have demonstrated to modulate innate immunityin goats and cows. Galectin acts as PRR; thus, it can identify PAMPs by binding microorganism-specific glycan of micro organisms and begin host immune responsesby modulating host cells such as neutrophils, macrophages, eosinophils, mast, and dendritic cells remarkably [42,43]. Parity and periparturient period is the time when fertility, milk production, and inflammation in dairy cows, sheep, and goats are affected terribly. Hence, most of the studies on ruminants are performed during the periparturient period so that therapeutic targets such as galectins can be tapped [44]. Moreover, in periparturient goats and sheep, galectins have been found to regulate innate and adaptive immunity to combat immune suppression during the periparturient stage, which is highly susceptible to diseases [45]. In particular, gal-8 exhibited bovine neutrophil activation and migration through superoxide production as a potential therapeutic to reduce inflammation [8,46,47]. Adjei-Fremah et al. [48,49] reported that polyphenols extract from cowpeas can bind and regulate gene expressions of galectins in bovine inflammatory diseases. Besides, several plant extracts such as *Curcuma longa*, *Echinacea angustifolia,* and *Butea frondosa* have been used on sheep neutrophil to evaluate their anti-inflammatory and apoptotic modulation properties [41].

As an alternative non-chemical approach, [50] studied the effect of probiotics on lactating Holstein-Friesian cows and found that the lymphocytes count significantly increased with a percent decrease in neutrophil count in the treatment group. Probiotics serve as the non-pathogen associated molecular pattern; as a result, it promotes growth and rumen function in cows [51]. Moreover, probiotic treatment impacted three pathways remarkably, such as inflammatory response, TLR, and wingless signaling pathways.

Limitations

In ruminants, to cure nonspecific postpartum inflammation, specific pharmaceutical drugs have not yet been approved with dosage. On the other hand, due to the possible threat of antibiotic resistance against microbial agentsas well as its putative risk to access the human body through the food chain, the use of antibiotics is banned on livestock. In addition, the efficacy of NSAIDs administration on inflammation remained inconsistent. With some handful of positive effects including mastitis [52] and pregnancy rate at embryo transfer [53], most of the treatments exhibit the moderate or negative effect of NSAIDs on reproduction. During artificial insemination, the drug did not ameliorate the pregnancy rate [54] and insemination success rate at mid-luteal phase. Also, treatment before ovulation was baleful as the drug mitigated ovulation and follicular cyst formation [55]. Besides, studies on immunomodulation are at a novice stage and need in-depth study to implement on ruminants.

Potential interventions

There is a noticeable association between immunity and disease resistance as the frequency and duration of a disease are more likely to increase when an animal has weak immunocompetence [56]. Several studies have been conducted in ruminants encouraged by evidence that nutrition has an impact on immunity that plays a vital role to curb inflammationmore than vitamins and minerals. It has been reported that nutrients not only provide energy to the animals but also essentially required by leukocytes for proliferation and production of antibodies and APPs [56].

Moreover, after heavy restriction on the use of antibiotics as feed additives by European legislature (2003) and new Veterinary Feed Directives by United States (2017) on the use of medicated feed, numerous research programs have gained momentum towards phytochemicals based therapy to augment immune functionality of livestock [19,57]. Since then, plant bioactive enriched compounds were thoroughly investigated and justified the scope of alternative feed ingredients in the form of herbs, spices and plant extract to boost ruminant's immune health by exhibiting the immense potential to exert the same anti-inflammatory potency as a commercial drug without side effects.

Major Anti-Inflammatory Compounds of Plants, Herbs, and Spices

For thousands of years, mankind has been using plants and their byproducts as food and medicine. Plants have a tremendous ability to synthesize innumerable bioactive compounds with healing attributes; thus, they are of great significance for researchers. However, the majority of the compounds synthesized by plants fall under phenolic aromatic compounds or their oxygen substituted analogs. Most of the synthesized compounds of plants are secondary metabolites that play a pivotal role in the plants' defense mechanism. So far, nearly 12,000 secondary metabolites,which is merely 10% of their total metabolites count, have been isolated from plants [58]. Among the diverse range of compounds produced by plants, secondary metabolites ensure the defense mechanism of plants against pathogens, insects, and herbivores. In addition to physiological roles, quinones and tannins being colored compounds are associated with plant pigment, while terpenoids provide a unique aroma to the plants [59].

Phenolics and Polyphenols

The phenolic compounds and polyphenols are abundantly found in all plants. In the past few decades, these chemopreventive agents have received enormous attention because of their supreme anti-inflammatory, antioxidant properties, and other biological roles on animal's health [60]. Chemically, phenolics are the compound that owns an aromatic ring having one hydroxyl group, while polyphenols can have one or more aromatic rings with many hydroxyl groups [13]. These plant secondary metabolites are produced as a plants' defense mechanism against pathogens, as a result, have been explored for a variety of applications in animals including sheep, cows, and goats [61]. Alpha-tocopherol (vitamin E) is a known antioxidant that neutralizes ROS production and consequently obstructs the progression of inflammation. A study was found that the plasma concentration of α-tocopherol in cows was very low that indirectly associated with transition cow disorders [62]. Administration of α-tocopherol not only modulates inflammation by decreasing inflammatory cytokine production in transition cows but also ameliorates clinical mastitis, retained placenta, and liver function. [63,64] investigated the efficacy of polyphenol from cowpea in bovine blood and reported that it upregulated the expression of anti-inflammatory cytokine IL-10. In addition, cowpea polyphenols also mitigated the Wnt signalingpathway, which has been implicated in inflammation [65]. Crude polyphenols extract from Cherokee tomato significantly suppressed the transcription of cox-2 gene expression, thereby reducing inflammation and modulated innate immunity in cows [66].

Flavonoids

According to the number of phenol rings, polyphenols can further be categorized into flavonoids and non-flavonoids [68]. In flavonoids, fifteen carbons are uniquely organized in a C6-C3-C6 configuration having two aromatic rings (A & B ring) joined to a heterocyclic C ring. Hydroxylation pattern of C ring and its modification essentially determines the major classes of flavonoids such as flavones (one carbonyl group) and flavonols (3-hydroxyl groups) [19,67]. The supreme antioxidant and other biological activities of flavonoids are directly proportional to its structure as well as a higher degree of hydroxylation [68], and they are known to exert anti-inflammatory and anti-oxidative properties. Flavonoids have been found to inhibit the biosynthesis of prostaglandins through which they exert anti-inflammatory effects [69].

It has been monitored that during mastitis, TLR4-located receptors at mammary epithelial cells and resident leukocytes identify LPS, there by activating NF-κB mediated inflammatory response. [70,71] evaluated the effect of baicalein (flavones) and morin (flavonol) respectively on bovine mammary epithelial cells in *in vitro* studies and found mitigated action of NF-κB and mitogen-activated protein kinase. In particular, the phosphorylation of I κB and p65 were greatly suppressed by flavonoids, which in turn reduces NF-κB activation.

In addition, [71,72] reported that mRNA expression of proinflammatory cytokines was greatly diminished when the cells were treated with flavonoids. Also, heifers treated with flavonoid essential oil had reduced neutrophil blood concentration, LPS binding protein, and serum amyloid A than control heifer [73] suggesting that flavonoid-rich diets can ameliorate rumen fermentation and minimize the risk of acidosis. Administration of concentrate feed pellets containing fermented green tea probiotics, illite, and licorice to beef cattle from birth to post-weaning (60 days) did not modify leukocyte count [74]. Another piece of *in vitro* study on calves fed pomegranate extract demonstrated that blood mononuclear cells produced more IFN-γ and IL-4. Ovalbumin vaccine challenged calves fed pomegranate extract produced high anti-ovalbumin IgG compared to control [75].

Terpenes

Terpenes are plant secondary metabolites characterized by having predicated isoprene rings. The chemical conformation of terpenes is $C_{10}H_{16}$. They can be subdivided into diterpenes (four isoprene units), triterpenes (six isoprene units), tetraterpenes (eight isoprene units), hemiterpenes (single isoprene unit), and sesquiterpenes (three isoprene units) [76]. Terpenoids or isoprenoids are multicyclic and extensively branched structures with oxygen-containing functional groups chemically derived from terpenes [59]. Table 1 depicts that terpenes and terpenoids have been found to have nematocidal properties in ruminants [57,77].

Essential Oils

Essential oils (EOs) are enriched with terpenes. EOs are a liquid and volatile form of secondary plant metabolites produced from aromatic plants as herbs [78]. For the treatment of pain, inflammation, urinary tract infection, gastrointestinal disorders, and arthritis, ginger (*Zingiber officinale Roscoe*) has been used as a folk medicine for ages. Recently, eugenol (4-allyl-2-methoxyphenol)that is enriched with phenolic compounds has drawn huge attention from researchers. Eugenol has been used extensively in complementary therapies because of its plethora of healthy features. Eugenol is the bioactive compound of clove oil, also present in nutmeg, cinnamon, and basil have shown several beneficial attributes such asanti-inflammatory, antiparasitic, antimicrobial, and antioxidant activity [79]. Most cattle are fed with eugenol in combination with other oils, including cinnamaldehyde, and capsicum to ascertain the growth pattern [80], however, to explore its further immunomodulatory effect, in-depth study on ruminants are required.

Tannins

Tannins that are present in plant's leaves, fruits, roots, and bark, are water-soluble polymorphic phenolic compounds that can precipitate proteins from aqueous solution. Tannins can be classified into hydrolyzable (gallic acid or ellagic acid) and condensed tannin (catechin, epicatechin). Tannins can attach to polysaccharide and serve as a lethal agent to bacteria. Tannin-rich *Sericea Lespedeza* (SL) has been found very effective against the intestinal parasite,thus, its efficacy was evaluated in goat's blood, and it was found that SL modulated expression of genes implicated in the innate immune response. SL profoundly affected the release of pro-inflammatory cytokines such as TNF-α, IFNr, granulocyte colony-stimulating factor (GCSF), granulocyte-macrophage colony-stimulating factor (GMCSF), and decreasing IL8 and RANTES in the blood [81]. In addition, SL has found to trigger proinflammatory markers upon treated with PAMP (LPS and peptidoglycan) activated goat's blood [69].

Quinones

Quinones are a class of organic compounds aromatic rings with two ketone substitutions. Free radical production is considered as an important stage of the inflammatory response. Quinone can quench those free radicals, thereby preventing inflammation.

Alkaloids

Alkaloids are a class of nitrogenous organic compounds, from which isoquinoline, quinoline and indole alkaloids were studied the most for their anti-inflammatory activities.

In addition to the abovementioned bioactive compounds, there are thousands of other compounds that plants can synthesize such as saponins, lectins, polypeptides, polyamines, glucosides, and omega-3 fatty acids which exhibited potential roles as anti-inflammatory agents. Table 2 shows the effect of anti-inflammatory bioactive compounds from plants and their therapeutic potential on ruminants. In dairy cattle, the synergistic activity of green tea and Curcuma extract in milk were investigated during the transition that resulted in augmented milk yield (4.5L/day), reduced liver lipids, and plasma NEFA concentration after calving [82]. The less responsive immune system was noticed in cows when treated with omega-3 sources [83]. On the other hand, [84] fed fresh cows with whole flaxseed containing omega-3 fatty acids that outweighed omega-6 fatty acids by enhancing greater phagocytic activity of circulating leukocytes and plasma glucose with decreased plasma ketones. The plant extracts, rich in w3-polyunsaturated fatty acids (PUFA), linoleic acid, and antioxidants, such as Se, vitamin C, vitamin E, b-carotene, and polyphenols reported modulating various transcriptional factors like NF-kB and PPARa that in turn governs inflammation affecting genes [85].

[86] studied the efficacy of garlic (*Allium sativum*, L), eucalypt (*Eucalyptus globulus*), and *Gnaphalium conoideum* extract in Holstein cows suffering from acute endometritis. Among all three garlic extract effectively worked against endometritis followed by eucalypt. Also, garlic extracts remarkably alleviated gastrointestinal infections caused by Coccidia in adult female Boar goats [87]. In sheep, β-sitosterol mitigated high grain diet-induced inflammatory response and improved ruminal fermentation and microbiota by obstructing the attachment of LPS to TLR4 in the NF-κB pathways thereby reducing (TNF)-α, IL-1β and IL-6 levels [23].

No.	Plant/herbs/ spices	Bioactive compounds/chemical constituents of different plant species	Therapeutic attributes	References
1.	Astragalus	Astragalosides, Calycosin	anti-inflammatory, antioxidant, anticancer and antiviral properties	Gao et al . [94] Chen et al [93]
2.	Anise	Phenolics, Flavonoids, estragole	Anti- skin inflammatory, antiviral, Antifungal, antioxidant,	Craig et al. [92]
3.	Basil	Phenolics, Anthocyanin, Eugenol, methyl chavicol, linalool, isoeugenol, and methyl isoeugenol	anti-inflammatory, antioxidative properties, anticancer	Carrasco et al. [79]
4.	Black Pepper	Alkaloids (Piperine)	Anti-inflammatory, antimicrobial, immunomodulatory, anticarcinogenic, stimulatory, hepatoprotective,	Reddy et al [84] Joe et al [89]
5.	Capsicum	capsaicinoids (capsacicin), carotenoids, tocopherols,	antioxidants, anti-inflammatory, antiallergic, anticancer, antidiabetic, antibacterial	Compiani et al. [80] Reddy et al [88] Joe et al [89]
6.	Cinnamon	Cinnamaldehyde, procyanidins and catechins camphor, cinnamyl-acetate, caryophyllene, trans α-bergamotene, caryophillene oxide, linalool, geraniol, bornyl acetate, α-cubebene, γ-elemene, α-copaene, guaiol, and eugenol	anti-inflammatory, antimicrobial, antifungal, antioxidant, antidiabetic, antitermitic, nematicidal, mosquito larvicidal, insecticidal, antimycotic, anticancer properties	Compiani et.al. [80] Reddy et al. [88] Joe et al. [89]
7.	Chamomile	levomenol (α-bisabolol),apigenin, azulenes, farnesene, spathuleno, and spiroethers	antiinflammatory and antiseptic	Craig et al. [92]
8.	Clove	Eugenol, β-pinene, limonene, farnesol, benzaldehyde, 2-heptanone and ethyl hexanoate	anti-inflammatory, antitumor, antibacterial, antifungal, antipyretic, anesthetic, and analgesic activities	Carrasco et al [79] Compiani et al. 980]
9.	Cowpeas	Phenolic acids, flavonol glycosides, Tannins, Anthocynin	anti-inflammatory, antioxidative properties	Sarah et al. 2015, Sarah et al. 2016, Sarah et al. 2017
10.	Cumin	thymoquinone, thymohydroquinone, p-cymene, carvacrol, 4-terpineol, sesquiterpene longifolene	antioxidant, anti-inflammatory, neuroprotective, radioprotective, chemopreventive	Reddy et al. [88] Joe et al. [89]
11.	Cumin EO	Cuminaldehyde	Anti-inflammatory, antimicrobial, anti-oxidantive, anticarcinogenic,	Reddy et al. [88] Joe et al. [89]
12.	Essential Oils	Terpenes, sterols, carotenoids, flavonoids	antioxidant, anti-inflammatory, antimicrobial, and antifungal, anti-allergic, immunomodulatory properties,	Mahizan et.al. [78]
13.	Eucalyptus	essential oils, phenolic acids, flavonoids and hydrolysable tannins	anti-inflammatory, analgesic, antifungal, antibacterial, antidiabetic, antioxidative, antiviral, antitumor, antihistaminic, anticancer	Borges et al. [86]
16.	Flax seed	omega-3 fatty acid, alpha linolenic acid, the lignan secoisolariciresinoldiglucoside	anti-inflammatory, anticancer, antioxidant, immune boosting, antidiabetic, hepatoprotective, antifibrinolytic and antiplatelet aggregatory activity	Silvestre et al 2011, Gandra et al 2016, Bertoni et al 2015
17.	Garlic	allicin, alliin, diallyl sulfide, diallyl disulfide, diallyl trisulfide, ajoene, and S-allyl-cysteine	anti-inflammatory, antimicrobial, anticancer, antioxidant, immune boosting, antidiabetic, hepatoprotective, antifibrinolytic and antiplatelet aggregatory activity	Borges et al. [86] Worku et al. [87]
18.	Ginger	Phenolics (gingerols, shogaols, and paradols, quercetin), terpenes, Oleoresin	antioxidant, anti-inflammatory, antimicrobial, anticancer, neuroprotective, cardiovascular protective, respiratory protective, antiobesity, antidiabetic, antinausea, and antiemetic activities	Reddy et al. [88] Joe et al. [89]
19.	Ginsenosides	Saponins (glycosylated triterpenes)	anti-inflammatory, anticancer, antiaging, antioxidant, antiallergic, and antifatigue activities	Gao et al . [94]
20.	*Gnaphalium conoideum*	flavonoids, sesquiterpenes, diterpenes, triterpenes, phytosterols, anthraquinones, caffeoylquinic acid derivatives	anti-inflammatory, antioxidant, antibacterial and antifungal, anti-complement	Borges et al. [86]
21.	Green tea	catechin, gallocatechin, epicatechin, epigallocatechin, epicatechin gallate and epigallocatechin gallate	Anti-inflammatory, anti-oxidative properties	Winkler et al. [82]
22.	Licorice	flavonoids, saponoids, sterols, glycyrrhizin,isoprenylated phenolics	antioxidant, anti-inflammatory, anti-microbial, anti-viral, and anti-carcinogenic	Craig et al. [92]
23.	Marigold	gallic acid, scopoletin, ferulic acid, quercetin	anti-inflammatory, healing, and antiseptic property	Craig et al. [92]
24.	Nutmegs	flavonoids, alkaloids, steroids, saponins, tannins and phenolics	antioxidant, anti-inflammatory	Carrasco et al. [79]
25.	Phytosterols	B-sitosterol,campesterol stigmasterol	anti-inflammatory, antioxidants,	Xia et al. [23]
26.	Pomegranate	flavonoids, polyphenols, ellagitannins, and proanthocyanidin	anti-inflammatory properties, antioxidant, and anticarcinogenic	Oliviera et al. 2010
27.	*Sericea lespedeza*	Tannins	anti-inflammatory properties, antiparasitic	Worku et al. [87] Asiamah 2016 [51]
28.	*Sophora alopecuroides*	alkaloids, flavones, volatile oils, and quinones	anti-inflammatory, detoxification, anti-bacterial, anti-tumor	Liu et al. [95]
29.	Turmeric	Curcuminoids (curcumin, demethoxycurcumin, and bis-demethoxycurcumin)	anti-inflammatory, antimicrobial, antifungal, antioxidant, antidiabetic,	Winkler et.al [82] Reddy et al. [88] Joe et al. [89]

Table 1: Effect of anti-inflammatory bioactive compounds from plants and its Therapeutic potential

Serial No.	Nematicidal Plant species	Bioactive compounds	Nematodes	Ruminants
1.	*Alnnona squamosa*	terpenoids	*Haemonchus contortus*	Goats
2.	*Artemisia herva-alba*	terpenes	*H. contortus*	Goats
3.	*Chenopodium embrosioides*	terpene peroxide	*H. contortus*	Goats
4.	*Calotropis procera*	triternoids	*H. contortus*	Sheep
5.	*Butea monosperma*	terpene	*Caenorhabditis elegans*	-
6.	*Cymbogon martini*	terpene	*C. elegans*	-
7.	*Terminalia macroptera*	terpene	*C. elegans*	-
8.	*Artemisia sanctonica*	terpene	*Ascaris lumbricoides*	-
9.	*Inula helenium*	terpene	*A. lumbricoides*	-
10.	*Mentha cardifolia*	terpene	*Ascaris suum*	-
11.	*Ocimum gratissimum*	terpene	*Heligmosomoides polygyrus*	-

Table 2: Nematicidal properties of different plants

The bioactivity for anti-inflammatory effects of spice principles - curcumin, eugenol, linalool, zingerone, capsaicin, cuminaldehyde, and piperinewas studied and found highly effective (15-52%) in inhibition of carrageenan-induced inflammation in rats, [88,89]. Some researchers claim that the rich terpenoids and flavonoids contents in spices can subdue the synthesis of arachidonate metabolite and, eventually, the synthesis of prostaglandins that are considered to be potent inflammatory mediators. In addition, terpenoids and flavonoids also inhibit the secretion of lysosomal enzymes, for example, hyaluronidase, elastase, and collagenase enzymes by macrophage [90,91]. Some other herbs and spices are also enlisted, such as anis, licorice, marigold, and chamomile, whose anti-inflammatory perspective can be explored [92].

It is vital to mention that herbs and spices have ample amounts of biologically active flavonoids, terpenoids, vitamin C, and carotenoids. They remarkably exhibit immunostimulatory attributes that can ameliorate the function of lymphocytes, macrophages, and natural killer cells, thereby facilitating phagocytosis and interferon production [92]. Upon achyranthan and astragalan polysaccharides treatment, nitric oxide (NO), as well as the production of IL-2 in splenocyte, rapidly augmented [93]. Gao et al. [94] reported that ginsenosides and astragalus saponins intensified the phagocytic performance of reticulo endothelial cells that eventually boosted antibody production from B-lymphocytes. [95] found humoral immunity and cell-mediated immune response were elevated by alkaloids derived from *Sophora alopecuroides* that also fortified macrophage phagocytosis.

Conclusions

A growing number of researches on anti-inflammatory effects of plant-based bioactive compounds reflect that this field showed the immense potential to curb inflammation and boost the immune system without side effects. However, the amount of studies undertaken so far is inadequate to tap vast plant-based bioactive compounds that bear analogous attributes. Inflammation may play a vital role in the development of transition disorders and metabolic diseases. Therefore, research on plant-based bioactivesfor diseases/ metabolic disorders in combination with targeting immunomodulation could be a novel and wise approach to fight inflammation. Essential oil-based bioactives such as eugenol and cinnamaldehyde showed promising results to fight inflammation; hence they have tremendous potential to be used in immunomodulatory effects in ruminants. Also, targeting neutrophils using galectins can worth noting to explore its prospects as anti-inflammatory tools.Therefore, in-depth studies on the abovementioned aspects warrant to harvest the full efficacy of plant-based bioactives against inflammation and its allied complications.

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