Herbal Complement Inhibitors in the Treatment of Neuroinflammation

Future Strategy for Neuroprotection

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ABSTRACT: The upregulated complement system plays a damaging role in disorders of the central nervous system (CNS). The classical and alternate pathways are two major pathways activated in neuroinflammatory disorders such as Alzheimer’s disease, multiple sclerosis, traumatic brain injury, spinal cord injury, HIV-associated dementia, Parkinson’s disease, and mad cow disease. Failure of currently available anti-inflammatory agents, especially cyclooxygenase inhibitors, in offering significant neuroprotection in large epidemiologic clinical trials of CNS disorders suggests an urgent need for the development of new neuroprotective agents. The positive preclinical outcomes in treating CNS disorders by complement regulatory molecules, such as vaccinia virus complement control protein, suggest the possibility of using complement-inhibitory molecules as neuroprotective agents. Several active ingredients of herbal origin are found to have complement-inhibitory activity. These herbal ingredients along with other anti-inflammatory roles might be useful in treating neuroinflammation associated with CNS disorders. Active ingredients of herbal origin with complement inhibitory ingredients are summarized and classified according to their chemical nature and specificity towards the major pathways activating the complement system. The structure activity relationship of some specific examples is also discussed in this report. This information might be helpful in formulating a natural panacea against complement-mediated neuroinflammation.

KEYWORDS: neuroprotection; neurodegeneration; complement inhibitors; herbal ingredients; alternate pathway; classical pathway; cyclooxygenases; vaccinia virus complement control protein (VCP); Alzheimer’s disease (AD); HIV-associated dementia (HAD); Parkinson’s disease (PD)

THE COMPLEMENT SYSTEM IN NEURODEGENERATION

The complement system is known to perform a wide range of functions in the human body. It forms an essential component of the host immune system and is...
associated with the clearance of molecules of foreign origin as well as the elimination of invading pathogens from the body. It plays an important role in adaptive immunity. However, it is nonspecific in action and unable to distinguish between self and non-self. Under normal conditions, it is strictly regulated by complement regulatory molecules. However, in neuroinflammatory disorders, the complement regulatory molecules fail to control the activated complement components. These activated complement components then act as a double-edged sword and are responsible for the degeneration of neurons. The devastating roles of the complement components in neurodegenerative disorders are well documented. Alzheimer’s disease (AD), multiple sclerosis (MS), myasthenia gravis, Parkinson’s disease (PD), traumatic brain injury (TBI), and spinal cord injury (SCI) are examples of a few disorders in which activated complement components play an important role. Not only do these disorders arise out of dysfunction in the normal metabolic machinery, but also neuroinflammatory disorders associated with microbial infections show involvement of complement components. In HIV-associated dementia (HAD), complement components are responsible for neuroinflammation. HIV-1 and its pathogenic proteins such as GP-120, GP-41, and Nef-1 are also associated with the activation of complement components. HIV-1 along with the aforementioned pathogenic proteins is also known to modulate the C3 promoter activity in neurons and/or astrocytes. HIV has developed an effective evasion strategy involving synthesis of HIV-associated molecules from complement-mediated damage. It also utilizes the complement opsonins in the process of cell entry and replication. This whole phenomenon is outlined in a recent review by Stoiber et al.

Spongiform encephalopathies such as scrapie, are also associated with the activated complement components. The complement system is activated by the three major pathways, the classical pathway (CP), alternative pathway (AP), and lectin-mediated pathway. Activation of one of the pathways may lead to activation of the other pathway. The C3b component generated by spontaneous activation of the CP leads to activation of the AP by formation of the alternate pathway C3 convertase. These pathways lead to the generation of opsonins and anaphylatoxins. The final common step after activation of the complement system is the generation of the membrane attack complex (MAC). The complement anaphylatoxins are responsible for the various proinflammatory events in the CNS and chemotaxis of the immunocompetent cells. The brain environment is further complicated by release of proinflammatory mediators such as nitric oxide and glutamate. Mast cells are found in the brain and in the proximity of neurons. Anaphylatoxins and other mediators may activate secretion of proinflammatory molecules from the mast cell. The C3a is found to be involved in the activation of the mast cells through FcγRI receptors. Anaphylatoxins are also known to activate brain astrocytes through C3a and C5a receptors located on them, resulting in release of cytokines and chemokines involved in the pathogenesis of CNS disorders. One of the complement components, C5b-9, is also known to activate prostaglandin production in glomerular epithelial cell (GEC) injury. C5b-9 upregulates the cyclooxygenase-2 enzyme (COX-2) in GEC. COX-2 is found to be associated with the complement components in the brain. It selectively activates the C1q component of complement in the brain. MAC induces concentration-dependent neuronal cell death and changes in membrane permeability to Na⁺, K⁺ and Ca²⁺, release of cytokines, eicosanoids, and reactive-free radicals. These changes occur at
sublytic concentrations of MAC.$^{23}$ MAC is also responsible for the demyelination of neurons in demyelinated forms of certain disorders.$^{24}$

It is therefore well established that inflammation plays a major role in the etiology of neurodegenerative disorders and that complement components are one of the major groups of proinflammatory molecules that are involved.

**CURRENT ANTI-INFLAMMATORY AGENTS**

Although, inflammation plays an important role in CNS disorders, no currently available anti-inflammatory agent offers significant neuroprotection in such disorders. Anti-inflammatory agents used in therapy can be broadly classified as steroidal and nonsteroidal agents (SAIDs and NSAIDs, respectively). These drugs pose potential health hazards in long-term treatment. The role of steroidal agents such as estrogen in the treatment of dementia is controversial and is not recommended for age-associated dementia.$^{25}$ Treatment with a combination of estrogen and progestin causes a cognitive decline in postmenopausal women.$^{26}$ Prednisolone treatment also failed in clinical trials of AD.$^{27}$

NSAIDs are either nonspecific inhibitors (mixed; inhibit both cyclooxygenases, COX-1, and COX-2) or specific inhibitors (generally target COX-2). Both are associated with adverse effects. Nonspecific NSAIDs such as indomethacin are associated with gastric mucosal damage and aggravate the problems associated with *Helicobacter pylori*.$^{28}$ Recently, a selective COX-2 inhibitor vioxx (rofecoxib) was removed from the market because of the cardiotoxicity associated with its use. Mixed NSAIDS and rofecoxib are associated with congestive heart failure (CHF) and hypertension.$^{29}$ Whether the risk of heart disease is associated with COX-2 inhibition or to the unique structure of rofecoxib still remains controversial. Further research is needed in the use of these drugs, and it is best to avoid using these agents in such disorders. COX inhibitors are associated with the risk of myocardial infarction,$^{30}$ edema, and hypertension.$^{31}$ Selective COX-2 inhibitors show similar adverse drug-related events as demonstrated by nonselective NSAIDs treatment.$^{32}$ Previously, COX-2 expression was considered inducible, but recent evidence suggests that it is constitutive in the brain. It is expressed by neurons and plays a critical role in coupling synaptic activity to neocortical blood flow.$^{33}$ COX-2 in the brain is the primary isozyme involved in memory consolidation, and COX-1 is associated with memory formation.$^{34}$

Controversies regarding the role of COX-2 in CNS disorders, its beneficial roles in normal cognitive function as well as the adverse effects of NSAIDs in the brain are discussed in a recent review by Minghetti.$^{35}$ COX inhibitors are not only responsible for the generation of harmful prostaglandins, but also involved in the generation of PGE$_2$, which is known for its involvement in potential beneficial effects, such as membrane excitability and synaptic transmission in the hippocampus,$^{36}$ and neuroprotection against TNF-$\alpha$. Thus, inhibition of COX attenuates the potential beneficial roles of PGE$_2$. Recent large-scale randomized controlled clinical trials with NSAIDs in the treatment of CNS disorders yielded poor results.$^{38-40}$ However, indomethacin was found to be beneficial in mild cognitive impairment and nimesulide was also found to be effective.$^{41,42}$ Their beneficial effects can be attributed to actions other than COX inhibition.
The reason for the failure of these agents in the treatment of neuroinflammatory disorders can be attributed to their inability to target the key component involved in neuroinflammation. Also, most of them target cyclooxygenases, whose roles in the CNS are controversial. Complement plays an important role in the etiology of almost all CNS disorders, as outlined previously in this review. The role of the complement components in neuroinflammation, the interaction with other proinflammatory molecules, and the need for complement inhibition are outlined in a recent review by Kulkarni et al.43

**COMPLEMENT INHIBITORS IN NEUROINFLAMMATION**

Preclinical outcomes from our laboratory suggest that complement regulatory molecules might be of great help in the treatment of the aforementioned chronic neuroinflammatory disorders. Vaccinia virus complement control protein (VCP) was found to be effective in treating SCI and TBI.44–46 It might be useful in the treatment of CNS injury associated with AD.47 sCrry is another complement regulatory molecule found to be effective in the treatment of allergic encephalomyelitis.48 However, no complement inhibitory molecule is currently available on the market for the treatment of neuroinflammatory disorders. Complement inhibitors are relatively new in drug therapy. Certain pharmaceutical companies are targeting the complement inhibitors for the treatment of disorders such as rheumatoid arthritis and cardiovascular disease.49,50 The complement inhibitory molecules under development are pexelizumab and eculizumab. These monoclonal antibodies specifically target C5a, a potent anaphylatoxin, and are currently undergoing clinical trial.49,50 Recently, pexelizumab reduced the myocardial infarction and death rate in patients who had undergone coronary artery bypass graft surgery.51,52 However, their potential in neurodegenerative disorders and their bioavailability in the brain have yet to be investigated.

**HERBAL COMPLEMENT INHIBITORS**

During the last two decades, several ingredients of herbal origin have been tested for their complement inhibitory potential. To gain some perspective with a view to developing suitable complement inhibitory molecules from naturally occurring compounds, some of the active constituents of medicinal plants with complement inhibitory activity (in vitro in most cases unless mentioned) are discussed below. However, none of these agents has been tested clinically for its ability to offer neuroprotection.

**MEDICINAL PLANTS WITH COMPLEMENT INHIBITORY INGREDIENTS**

*Juglans mandshurica*. This plant consists of four flavonoids and two galloyl residues. The flavonoids with the most potent complement inhibitory activity found in this plant are afzelin and quercitrin. However, the galloyl residues, tetragalloyl glu-
cose and trigalloyl glucose, were more potent than the corresponding flavonoids. The tetragalloyl residue (1, 2, 3, 4 tetragalloyl glucose) was the most potent, suggesting the importance of the galloyl moieties in complement inhibition. 53

Glycyrrhiza glabra. This is an ancient Ayurvedic medicine known for its anti-inflammatory potential. The constituents, β-glycyrrhetinic acid and glycyrrhizin, were found to have complement inhibitory potential. Both of them induced conformational changes in C3. 54 β-glycyrrhetinic acid was more potent among them. It inhibits the CP at the level of C2 rather than C4 and C1q. 55 Glycirrhizin inhibited the C3 component of the complement anaphylatoxin C3a and C3b. 54 Apart from direct actions, these compounds are known to have some indirect anti-inflammatory activities, which make them suitable for the treatment of several inflammatory and autoimmune disorders.

Crataeva nurvala. The triterpene lupeol is an active constituent of this medicinal plant. Both lupeol and a compound synthesized from it, that is, lupeol linoleate, were found to have anti-inflammatory potential in adjuvant-induced arthritis in rats, the latter being more potent than the former. The anti-inflammatory activity can be attributed to the complement inhibitory activity of these compounds. The compounds were considered to reduce C3 convertase activity. The anti-inflammatory activity of these compounds was more than that of indomethacin; however, further elaboration of the complement inhibitory activity is essential. 56

Ligustrum vulgare and Phillyrea latifolia. Leaves. These belong to the Oleaceae family. The ethanolic extracts of both plants were found to have more complement inhibitory activity than the methanolic extract. The flavonoids apigenin, luteolin, and their glucosides, are the active constituents of these plants. The flavones showed dose-dependent inhibition of the CP. However, no such correlation was found with the AP. Further SAR studies revealed that in case of the glucosides, that is, apigenin-7-O-derivatives, complement inhibitory activity was optimum with disaccharide derivative. 57

Morinda morindoides. This is the most popular medicinal plant in the Democratic Republic of Congo and is used traditionally to alleviate rheumatic pain. Iridoids are active ingredients of this plant. Gaertneroside, acetylglaertneroside, and gaertneric acid inhibited the CP (in vitro action). Gaertneroside was the most potent among these compounds. Iridoids failed to inhibit the AP. 58 Apart from iridoids, Morinda also shows quercetin and other complement inhibitory molecules. Quercetin and MO15 inhibited both the AP and the CP. Others showed a more pronounced and dose-dependent effect on the CP. 59

Osbeckia aspera. The mature leaves of this Ayurvedic medicinal plant have been used traditionally to treat liver disease in Sri Lanka. The herb has immunosuppressive capabilities through other mechanisms apart from complement inhibition. The whole plant extract was found to have a dose-dependent effect on both the CP and the AP. The effect was more pronounced on the CP. 60

Cedrela liloi and Trichilia elegans. These medicinal plants, belonging to the Meliaceae family, grow in Argentina. The fresh leaf extracts of these two plants were found to have anticomplement activity. The extracts inhibited both the CP and the AP of complement activation. However, the chemical moieties responsible for this and the precise mechanism of complement inhibitory action of these plants are yet to be identified. These plants are also known to inhibit the phagocytosis of the peritoneal macrophages and possess strong antiproliferative activity against T cells. 61
### TABLE 1. Medicinal plants with complement inhibitory active ingredients: systematically outlined medicinal plants with complement inhibitory constituents along with their pharmacological actions on the complement system

<table>
<thead>
<tr>
<th>Medicinal plants</th>
<th>Active ingredients</th>
<th>Actions on complement system</th>
<th>Refs.</th>
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<tbody>
<tr>
<td><em>Wedelia chinensis</em></td>
<td>Wedelosin and others</td>
<td>Inhibits CP and AP</td>
<td>66</td>
</tr>
<tr>
<td><em>Persicaria lapathifolia</em></td>
<td>Kaempferol glycoside and acylated quercetin glycosides</td>
<td>Inhibits CP at 4.3, 9.7, 3.9, and 7.6 × 10^(-5) M, respectively</td>
<td>67</td>
</tr>
<tr>
<td><em>Rosmarinus officinalis</em></td>
<td>Rosmarinic acid</td>
<td>Inhibits CP and AP; binds C3, inhibits C5 convertase at a very high concentration</td>
<td>68,69,70</td>
</tr>
<tr>
<td><em>Petasites hybridus</em></td>
<td>Ze 339 and sesquiterpin ester petasin</td>
<td>Abrogates C5a-induced increase in calcium concentration</td>
<td>71</td>
</tr>
<tr>
<td><em>Soyabean oil emulsion</em>(Intralipid)</td>
<td>–</td>
<td>Inhibits <em>in vitro</em> synthesis and secretion of C4 and C2 by guinea pig peritoneal macrophages</td>
<td>72</td>
</tr>
<tr>
<td><em>Jatropha multifida latex</em></td>
<td>Polymer proanthocyanidin</td>
<td>Only CPI (<em>in vitro</em>); action is mediated by Ca^{2+} depletion</td>
<td>73</td>
</tr>
<tr>
<td><em>Aloe vera</em> (leaf parenchyma gel)</td>
<td>Polysaccharide with dominant mannose</td>
<td>Inhibits AP</td>
<td>74,75</td>
</tr>
<tr>
<td><em>W. fruticoso</em> <em>(Nimba arishta)</em></td>
<td>–</td>
<td>Complement inhibitory activity</td>
<td>76</td>
</tr>
<tr>
<td><em>Jatropha curcas L.</em></td>
<td>Curacycline A</td>
<td>Moderately inhibits CP</td>
<td>77</td>
</tr>
<tr>
<td><em>Centaurium spicatum</em></td>
<td>Quercetin derivatives</td>
<td>Complement inhibition: maximum in triacylated compounds</td>
<td>78</td>
</tr>
<tr>
<td><em>Piper kadsura</em></td>
<td>Piperlactam S</td>
<td>At 1-30 µm conc, inhibits C5a-induced migration, C5a-stimulated TNF-α and TNF-β</td>
<td>79</td>
</tr>
<tr>
<td><em>Lithospermum euchromum</em></td>
<td>LR-polysaccharide Ila</td>
<td>Inhibits CP and AP</td>
<td>80</td>
</tr>
<tr>
<td><em>Olive</em> <em>(Olea europaea L.)</em> leaves.*</td>
<td>Apigenin and other flavonoids</td>
<td>Inhibits CP</td>
<td>81</td>
</tr>
<tr>
<td><em>Crataegus sinaica</em></td>
<td>Whole extract</td>
<td>Inhibits CP and AP</td>
<td>83</td>
</tr>
<tr>
<td><em>Osbeckia octandra,</em> <em>Melothria maderaspatana,</em> <em>Phyllanthus debilis leaves</em></td>
<td>AR-arabinogalactan</td>
<td>Inhibits CP and AP</td>
<td>84</td>
</tr>
<tr>
<td><em>Angelica acutiloba</em></td>
<td>Fucans</td>
<td>Inhibits CP and AP</td>
<td>85</td>
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Azadirachta indica. This is commonly known as Neem in India and is well known for its medicinal value. The crude aqueous extract of the plant consists of complement inhibitory polymers NB-I and NB-II, the former being less active than the latter. Activity could be correlated with molecular weight, as NB-I, a high molecular weight compound, was less active than the low molecular weight compound NB-II. Glucose was found to be the main carbohydrate constituent. 62

Tinospora cordifolia. This climbing shrub, commonly called gurcha, is well documented in the Ayurvedic literature and is known for its anti-inflammatory and immunomodulatory potential. These constituents were also found to mediate phagocytosis by peritoneal macrophages. However, the two compounds, syringin and cordiol, inhibited the activation of the complement by inhibiting the C-3 convertase of the CP. Like the other active constituents, these were also found to potentiate the immune response. 63

Isopyrum thalictroides. This plant is used in Chinese medicine in the treatment of inflammatory disorders such as rheumatism, neuralgia, and silicosis. The plant with several photoberbezines and bisbezylisoquinoline (BBI) alkaloids having complement inhibitory activity may provide novel complement inhibitory molecules. However, isopyruthaline (It1), fangchinoline (It2), and isotalictrine (It3) are the three major active ingredients of this plant, whose complement inhibitory activity has been well studied. These constituents were found to inhibit the CP. It3 was the most potent inhibitor of the CP and It1 the least potent. It showed Ca$^{2+}$- and Mg$^{2+}$-dependent complement inhibition. It inhibited the formation of the first component of the complement system. The complement inhibitory actions of It2 were independent of Ca$^{2+}$ ions, and in the case of It3, its effectiveness decreased at a very high concentration of calcium ions. 64

The BBIs affected the formation of convertase and did not inhibit the decay of the convertase. These iridoids also influenced the AP. 65 It3 was found to suppress both pathways, but It1 and It2 augmented AP hemolysis at a higher concentration.

Apart from these specific plants listed with potent complement inhibitory molecules, the active ingredients of several other medicinal plants with known anti-inflammatory activity have shown inhibition of the complement system, as outlined in Table 1. These herbal ingredients are systematically classified on the basis of

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<td>Ascophyllum nodosum (brown seaweed)</td>
<td>Aqueous leaf extract</td>
<td>In vitro complement inhibition; tested in respiratory burst / in vivo zymosan-induced inflammation model</td>
<td>86</td>
</tr>
<tr>
<td>Trichilia glabra</td>
<td>Water-soluble extract: Sesquiterpenes quinines, coumarins, and flavonoids</td>
<td>More pronounced inhibition of CP than AP</td>
<td>87</td>
</tr>
<tr>
<td>Propolis V</td>
<td>Whole extract</td>
<td>Inhibits CP and AP</td>
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Apart from these specific plants listed with potent complement inhibitory molecules, the active ingredients of several other medicinal plants with known anti-inflammatory activity have shown inhibition of the complement system, as outlined in Table 1. These herbal ingredients are systematically classified on the basis of
their complement inhibitory activity (in vitro and/or in vivo in a few cases) and chemical nature. With an aim to develop either specific or nonspecific inhibitors of the complement system, these agents are also classified according to their mode of action. The compounds with novel action on the complement components are listed separately. Classification according to chemical nature might be of great help in developing structurally related potent complement inhibitory agents with neuroprotective roles.

**CLASSIFICATION AS PER MODE OF ACTION**

As discussed previously, the AP and CP are the two major pathways of complement activation involved in neuroinflammatory disorders. Thus, herbal complement inhibitors (HCIs) can be broadly classified as selective inhibitors (SIs) and nonspecific inhibitors (NSIs) of the complement system depending on their ability to inhibit one or both pathways involved in complement activation. SIs can further be classified as classical pathway inhibitors (CPIs) or alternate pathway inhibitors (APIs). Nonselective inhibitors can be classified as strong CP–moderate AP inhibitors (SCP-MAPs), strong AP–moderate CP inhibitors (SAPMCPs), and general complement inhibitors. The ingredients included in the general complement inhibitors section may inhibit one of the pathways to a greater extent than the other, but they can be considered as potent inhibitors of both pathways. This type of classification may help to select suitable complement inhibitory molecules based on the etiology of the disease. As discussed previously, activation of one pathway leads to activation of the other. Thus, depending on disease status, SIs and NSIs can be used in therapy. These agents are outlined in Figure 1. Apart from these compounds, novel complement inhibitors are outlined separately in Figure 2.

Understanding the mode of action of the individual agent might be of great help in developing an effective combination therapy using different complement inhibitory molecules targeting different complement components. This might also prove useful in avoiding irrational combinations. Hence, the actions of herbal ingredients on the complement components are represented diagrammatically in Figure 3.

**CLASSIFICATION ACCORDING TO CHEMICAL NATURE**

The ingredients of herbal origin can be grouped into several classes, based on their chemical origin. Most compounds inhibiting the complement components are either flavonoids and their glucosides,$^{53,66,67,78,81}$ polysaccharides,$^{74,75,80,84}$ or terpenes.$^{56,71,87}$ Apart from these major chemical classes inhibiting complement, other classes of complement inhibitors include iridoids,$^{58}$ polymers,$^{62,73}$ peptides,$^{77}$ alkaloids,$^{79}$ and oils.$^{72}$ These are outlined in Figure 4.

Synthesis of new structurally related analogs, systematic comparative study of these compounds and study of the bioavailability to the brain will reveal the novel complement inhibitory molecules with potent antineuroinflammatory activity. These neuroprotective agents will be of great help in the treatment of complex brain disorders such as AD, HAD, and PD.
Flavonoids and Derivatives

(a) The presence of the galloyl group increased the complement inhibitory activity of the flavonoids.
(b) Tetragalloyl glucose showed better activity than did trigalloyl glucose.
(c) There was an increase in anticomplement activity in inverse proportion to the number of free hydroxyl groups on the B-ring and 3,5,7-trihydroxyflavone.53
(d) In L. vulgare, triglucosides of the flavonoids were more active than those of the corresponding flavonoids.
(e) In apigenin-7-O derivatives, optimum activity was observed in a disaccharide derivative, and activity was reduced in the trisaccharide derivative.57

(f) In *M. morindoides*, mixtures of compounds were more active on the CP than were individual components.59

**Steroid-Like Compounds**

(a) The only representative of this class, β-glycirrhetic acid, showed confirmation-dependent complement inhibition. α-Glycirrhetic acid was found to be inactive.

(b) Substitution of the hydroxyl group at the C3 position of the first ring of the compound showed a decrease in activity. The derivatives glycyrrhizin and carbenoxolone sodium were found to be less potent than β-glycirrhetic acid.55

**Fucans**

(a) Fucan fragments (molecular weight range 4,100–21,4000) inhibited complement activation.

(b) There was an increase in complement inhibitory activity with increasing molar ratios of xylose, galactose, and glucuronic acid in fucans.

(c) Sulfate groups were necessary, but not sufficient for the complement inhibitory activity of fucans.

(d) The low molecular weight fucan (4,100) did not inhibit the AP.

(e) The glycosidic regions involved in the inhibition of the CP and AP might not be the same.85
FIGURE 3. Action of HCIs on different complement components. The CP gets activated by the antigen antibody complex and the AP by the polysaccharides or other activators. Also, activation of one of the pathways may lead to the activation of the other pathway. After being activated, these pathways lead to the generation of complement opsonins (C3b, iC3b, C4b, etc.), anaphylatoxins (C3a, C4a, and C5a), and MAC. More than 30 different complement proteins are involved in the process. The constituents of herbal origin inhibit one or more components of the complement system and thereby prevent the activation of complement pathways. The complement cascade, and actions of herbal ingredients on complement components are outlined in this figure. (———), complement pathway; (-----), synthesis and release of the complement components; (………), drug action; (□□□□□), inhibition of the pathway, complement component (or binding of a drug to a particular component), and/or synthesis and release of complement component by drug molecules; (○) anaphylatoxins.
FIGURE 4. Classification of HCIs based on their chemical structure. The ingredients of herbal origin can be grouped according to their chemical structures as outlined in this figure. Majority of the compounds, which inhibit the complement system are flavonoids, terpenes and polysaccharides.
CONCLUDING REMARKS

This review focuses on the detrimental roles of the complement system in neuro-inflammatory disorders and the inability of the currently prescribed NSAIDs to prevent and treat such disorders. The unavailability of a suitable complement inhibitory molecule in the market leaves an urgent need for the development of suitable complement inhibitory molecules with neuroprotective values. Complement inhibitory molecules of herbal origin, classification based on their mode of action on one or more complement components, and classification based on chemical structure and specificity and selectivity towards the particular complement component are discussed. Also, SAR studies of some of the complement inhibitory molecules are outlined. This collective information, that is, the devastating roles of the complement system along with information on herbal complement inhibitors, may shift the focus of scientists from the currently prescribed NSAIDs towards the complement inhibitory molecules. Complement inhibitory molecules may emerge as a separate class of antineuroinflammatory molecules. The SAR study outlined here may be helpful in the development of suitable complement inhibitors with neuroprotective abilities. Information on the mode of action of complement inhibitors might prove of significant help in designing a combination therapy with two or more agents with different modes of action on the complement system. However, rigorous research in this field with special emphasis on bioavailability to the brain, safety studies, separation of impurities, and clinical trials of the complement inhibitory molecules is essential in advocating herbal complement inhibitors as the next generation of neuroprotective agents.

SUMMARY

The currently existing NSAIDs are associated with side effects, and epidemiologic trials suggest their inability to offer significant neuroprotection. The positive preclinical outcome of the complement regulatory molecules, such as VCP, in treating neuroinflammatory disorders suggests their usefulness in CNS disorders, where complement plays a major role. In the last two decades, active ingredients and extracts of traditional medicinal plants with anti-inflammatory activity have been tested for their in vitro complement inhibitory activity. The classification, based on their mode of action (selectivity), chemical nature, action on individual complement components, and SAR studies discussed in the review may provide insight into novel complement inhibitors in the future. Systematic pharmacokinetic study of these herbal ingredients may also reveal complement regulatory compounds, which possess the ability to cross the blood-brain barrier. Thus, medicinal plants and their active ingredients with complement inhibitory activity (as discussed in this review) might prove beneficial in formulating a natural panacea against complex brain disorders.

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