

The Therapeutic Role of Alkaloids in Autoimmune Diseases

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ABSTRACT

Alkaloids are medicinal compounds derived from plants and have protective role against biotic and abiotic stress condition. For their antioxidant, anti-inflammatory, and anticancer properties, variety of alkaloids had utilized in popular medicine with the extension of human civilization history and until recent day. Great number of plants have abundant alkaloids within their secondary metabolites, some are edible and used in the daily diet such as legumins and nightshades, numerous are found in herbs and use widely in primary health care such as opium poppy. In the current review, we highlighted a potential therapeutic role of alkaloids classes on number of common autoimmune disorders which are considered chronic diseases affects immune system dynamics due to multifactorial process. Promising results from exhibited studies place alkaloids within important phytochemicals that have future pharmacological role in addition to their therapeutic role.

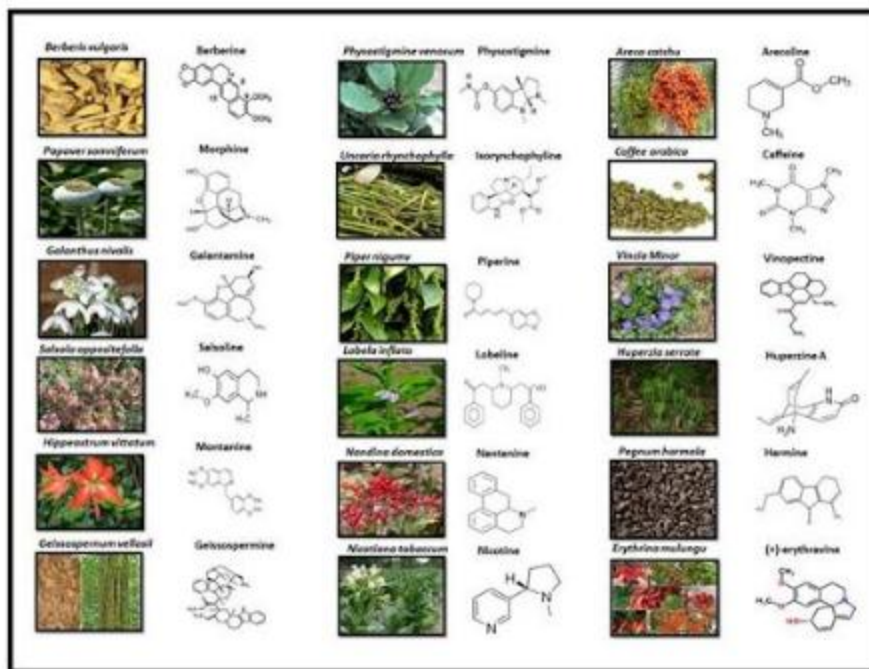
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INTRODUCTION

The Plant, a vivid picture of the presence of life on earth, is considered a main source of alkaloids in addition to fungi, bacteria and animal sources. Alkaloids are secondary metabolites that are widely distributed in the plant kingdom, predominately present in higher plants such as those belonging to the Ranunculaceae, Leguminosae, Papaveraceae, Menispermaceae, and Loganiaceae families (1). Under normal circumstances, alkaloids are not produced in plant in high quantities. However, secondary metabolites, including alkaloids, can be increasingly generated in response to biotic and abiotic stresses such as temperature, drought, irradiance intensities, soil nutrient composition, herbivores and pathogens. The generation of secondary metabolites acts as an important method for adaptation and species maintenance during the life time of the plant, especially in establishing ecological relationships between the plant and other organisms (2, 3). Importantly, alkaloid accumulation is a result in the response to developmental signals, such as changes associated with flowering and fruiting (4). Because bioactive alkaloids act to elicit specific plant responses, the production of these compounds is increasingly employed on a large scale as a continuous, reliable and renewable source, oftentimes using in vitro cell or organ culture, especially root tissue culture (5). Major research efforts have also been focused on the large-scale production of metabolites, including alkaloids, in bioengineered microorganisms by introducing plant alkaloid biosynthetic pathways in bacteria or yeast (6).

During alkaloid metabolism, primary nitrogenous metabolites including amino acids such as lysine, tryptophan, tyrosine and phenylalanine serve as necessary precursors for alkaloids and the chemical structure is often maintained within the nitrogen of the alkaloid molecule from within was derived. Nitrogen is a key component of alkaloids, and at least one nitrogen atom which in one or more heterocyclic ring structures is a general trait of alkaloids. The properties of different alkaloids are governed by the changing of nitrogen position in the carbon ring or molecule.(7). It was found nearly 20% of plant species contains alkaloids, plants use alkaloids as (i) competitive weapons against other bacteria, fungi, plants, insects, and large animals; (ii) transporting metal; (iii) agents for symbiotic relationships between microbes, plants, nematodes, insects, and higher animals; (iv) sexual hormones; and (v) effectors of differentiation (8). Alkaloids are classified into several classes based on their sources, biogenesis, and biosynthetic and chemical structures (Fig 1).

A



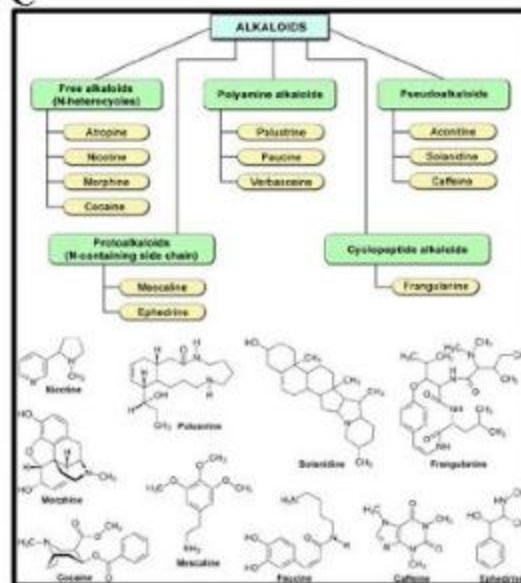
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Alkaloid	Origin	Example	Biological structure	Biological significance
True alkaloid	Derived from amino acids that have nitrogen in heterocyclic ring	Atropine		Anticholinergic (Ziegler and Facchini 2008)
Proto alkaloid	Derived from amino acids that don't have nitrogen in heterocyclic ring	Taxol		Used for treating ovarian, breast, and lung cancer (McGaire et al. 1989; Zasadil et al. 2014)
Pseudo alkaloids	Not derived from amino acids but have nitrogen in their heterocyclic ring	Caffeine		Antioxidant and anti-inflammatory (Hernan and Hernan 2013)

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Figure 1: Classification of alkaloids according to (A) plants sources (B) biogenesis (C) biosynthetic and chemical structures.

The mammalian immune system can mount two types of responses; the innate response and the adaptive response. Broadly defined, the innate immune system includes all aspects of host immune defense mechanisms consisting of physical, chemical and cellular immediate and non-specific defenses against pathogens. Unlike the innate mechanisms of host defense, adaptive immune response is specific to the pathogen presented and becomes eminent

after several days as antigen-specific T and B cells undergo clonal expansion (9). When the immune system mistakenly attacks the body it results in autoimmune disease which affects immune system dynamics. Autoimmune disorders are thought to be caused by a multifactorial process including genetic predisposition, infections, environmental agents and stress (10-12). Currently, studies have shown that genetic predisposition accounts for approximately thirty percent of all autoimmune diseases. The other 70 percent are due to environmental factors, including toxic chemicals, dietary components, gut dysbiosis, and infections (13). Alkaloids are among the oldest medicines known to man; in ancient times they were widely employed and this use was abundantly recorded in the folk medicine of various ethnic groups (14, 15). Due to the important bioactive role of alkaloids in plants and the therapeutic role that play in numerous human autoimmune disorders, we have reviewed a number of autoimmune diseases that are effectively relieved by the use of alkaloids.

Neurodegenerative diseases

Neurodegenerative diseases (NDDs) of the central nervous system are often described as a selective loss of neurons or neuronal function. Studies have shown that physicochemical properties of proteins are commonly altered, causing deposition of these proteins in the human brain leading to neuronal degeneration (16). We have presented evidence for promising alkaloid therapies for two common neurodegenerative diseases: Alzheimer's disease and Parkinson Disease.

1- Alzheimer's disease (AD)

In AD, patients suffer from extensive neuronal loss which begins with progressive deterioration of memory, learning and other cognitive functions. Beta-amyloid peptide ($A\beta$) is a main component of the amyloid senile plaques that occur in AD development in the human brain (17). Aggregation of $A\beta$ causes metabolic dysfunction, oxidative stress, inflammation and consequently apoptosis of neuronal cells (18). Several studies found that plasma from AD patients lack specific antibodies; these predominantly conformation-selective antibodies against neurotoxic oligomeric and fibrillar $A\beta$ aggregates can be identified in the plasma and intravenous immunoglobulin (IVIg) from healthy individuals (19, 20). The last hypothesis whereby AD is initiated on a disruption of the blood-brain barrier (BBB) caused by either genetic or non-genetic risk factors. The BBB disruption leads to passage of proteins in cerebrospinal fluid (CSF) and cause autoimmune response against pyramidal neurons located in the allo- and neocortical structures involved in memory forming and storage (21, 22). Within the isoquinoline class of alkaloids is Berberine (BBR) a relevant molecule in pharmacology and medicinal chemistry (23). The basic structure of isoquinoline is derived from tetrahydroisoquinoline, which can be modified in complex structures that can be all biosynthetically derived from phenylalanine and tyrosine. Isoquinoline can be isolated from *Hydrastis canadensis* (Goldenseal), *Berberis vulgaris* (barberry), *Coptis chinensis* (copies or golden thread) and *Berberis aristata* (tree turmeric) (17). In addition to the antimicrobial and antiprotozoal activities of BBR against different types of infectious organisms, studies report that BBR prevents $A\beta$ aggregation by reducing the activity of BACE-1 enzyme which is responsible for $A\beta$ initiation (24). Furthermore, BBR inhibit monoamine oxidase (MAO) and acetylcholinesterase (AChE) enzymes that involved in the advancement of AD which suggest a multitargeted approach for the disease's treatment (25, 26). Galantamine is another member of isoquinoline family and one of the most important derivatives compound with great therapeutic value for AD treatment. Galantamine can be isolated from *Galanthus woronowii* and *G. nivalis* and some *Narcissus* and *Leucojum* spp. of Amaryllidaceae. This compound is reported to be efficient selective to AChE (27). Galantamine inhibits the breakdown of Acetylcholine (ACh) by binding competitively and reversibly to the active site on AChE, the inhibition effects of galantamine on AChE is activated in the frontal cortex and hippocampal regions of the brain, the two areas in which cholinergic neurotransmission is most affected in patients with AD (28). New therapeutic treatments recently target multiple AD pathways to obstruction of AD progression, for this reason some isoquinoline and benzyloisoquinoline derivatives were considered potentially useful compounds. Alkaloids from *Colchicum speciosum* Steven (Colchicaceae), *Coptis* spp. (Ranunculaceae) and *Corydalis* spp. (Papaveraceae) act as AChE-inhibitors by different pathways (29). Epiberberine, pseudoberberine, and pseudocoptisine are examples of such compounds (30).

2- Parkinson Disease (PD)

Parkinson disease is the most common neurodegenerative disease that affects movement (31). One of the most important risk factors for PD is age (32). The male gender is also at higher risk (33). Environmental factors such as pollutants and cigarette smoking also increase risk for PD (34, 35). Regardless of cause, a defining feature of PD is a loss of dopaminergic neurons in the substantia nigra (SN) pars compacta (SNpc) which is located in the midbrain and plays an important role in reward and movement (36). Lewy bodies (LB) are intraneuronal, round, eosinophilic

inclusions associated with the pathology of PD and α -synuclein is a chief component of LB. A set of peptides derived from α -synuclein can act as antigenic epitopes and drive helper and cytotoxic T cell responses in patients with PD (37).

Therapeutic role of alkaloids in PD

Some studies have illustrated a therapeutic role for alkaloids in PD. Piperine (PIP) is one of alkaloids classes and present in the piper species, the fruit of black pepper (*Piper nigrum Linn*) and long pepper (*Piper Longum Linn*) (38), it has been reported to diminish inflammatory markers including interleukin-1 β (IL-1 β) and tumor necrosis factor- α (TNF- α) produced by Th-1 T-cells in an animal model of PD (39). Also, Piperine has been shown to have a wide range of activity, including monoamine oxidase MAO inhibition and penetration of blood-brain barriers (BBB) in a vitro study (40). Caffeine is another alkaloids class, belong to methylxanthine alkaloid and commonly found in tea, coffee, and cacao. Caffeine may confer neuroprotection against the underlying dopaminergic neuron degeneration, and influence the onset and progression of PD, as well can act as antagonist of the adenosine A2 receptor which has roles in inflammatory response, locomotor dysfunction, and tissue damage; resulting in attenuation of a suppressive effect of adenosine on brain dopaminergic transmission and neuronal cell death. Several randomized controlled trials have confirmed caffeine can improve the motor deficits of PD and that adenosine A2A receptor antagonists such as istradefylline reduces off time and dyskinesia associated with standard 'dopamine replacement' treatments. Finally, the potential role of caffeine in the management of non-motor symptoms of PD, which do not improve with the current dopaminergic drugs. (41-43).

Inflammatory bowel disease (IBD)

Inflammatory bowel disease (IBD) is commonly divided into two disorders: Ulcerative colitis (UC) and Crohn's disease (CD), both can be characterized as acute self-destructive inflammation in the gastrointestinal tract which can develop to chronic colitis and colon cancer (44). IBD is a complex disease caused by a combination of immune response, microbiota, environmental and genetic factors (45). IBD is controlled by a complex interplay of innate and adaptive immune response. Cytokines play a key role in influencing T cell differentiation to Th1, Th2, T regulatory and newly described Th17 cells which contribute to the development, recurrence and exacerbation of the inflammatory process in IBD (46). Current strategies to treat IBD often have adverse side effects and carry risk for serious treatment related complications (47).

Therapeutic role of alkaloids in Inflammatory bowel disease IBD

There is evidence for the anti-inflammatory properties of alkaloids in the treatment of IBD that is induced by TNBS or DSS in experimental animals. Berberine was recorded to remedy symptoms of IBD such as abdominal pain and diarrhea. As well, Berberine ameliorated DSS-induced body weight loss, myeloperoxidase activity, shortening of the colon, injury, inflammation scores and reduced proinflammatory cytokine levels in the colon, including TNF, IFN- γ , KC, and IL-17, proinflammatory cytokine production in colonic macrophages and epithelial cells as well as promoted apoptosis of colonic macrophages (48, 49). Berberine also ameliorated intestinal epithelial tight junction integrity in the colonic CACO-2 cell line and reduced epithelial gut permeability caused by cytokine-induced injury; TNF- α , IL-1 β , and INF- γ levels were influenced by Berberine administration and likely contribute to the effectiveness of Berberine in IBD (50). Similarly, the alkaloid Oxymatrine has been reported to reduce serum levels of TNF- α , IL-6, and the expression of NF- κ B, ICAM-1 in colonic mucosa which can ameliorate inflammation and thus alleviate diarrhea, bloody stool and histological signs of damage to colonic mucosa (51). Also, it has been shown that Oxymatrine can decrease the apoptosis index, intestinal lipid peroxidation, serum TNF- α levels, phosphorylated p38 mitogen-activated protein kinase (MAPK), and Fas/FasL expression (52) which all contribute to IBD severity.

Diabetes

Diabetes is a metabolic disorder, diagnosed by abnormalities in carbohydrate, lipoprotein and lipid metabolism, leading to chronic hyperglycemia together with other complications due to insulin deficiency or insulin resistance in the body. Based on the status of insulin in the body, as well as treatment, diabetes is mainly divided into three types; type 1 (T₁D): insulin dependent diabetes managed by insulin injection, type 2 (T₂D): insulin non dependent diabetes managed with healthy weight and exercise and third type: gestational, which can develop during pregnancy and goes away after the birth (53). T₂D is characterized as an autoimmune disorder; the risk of T₂D increases with body mass index and age (54). Abnormal accumulation of adipose tissue (AT) elevates the incidence of autoimmune diseases especially when AT is contiguous with main immune cell centers such as lymph nodes, thymus, and bone marrow; AT presence around the thymus may influence T cell differentiation in response to metabolic cues. Also, a large number of adipocytes reside in the bone marrow, and are probably involved in hematopoiesis, lymphopoiesis, and memory B and T cell responses (55, 56). Furthermore, B cells from diabetic patients, post stimulation, showed decreased secretion of the anti-inflammatory interleukin IL-10 which is also observed in other cell types when

exposed to the diabetic environment (57, 58). Th17/Treg and Th1/Treg were increased significantly in T₂D patients which consequently leads to increased INF-g and IL-17 secretion which promotes chronic inflammation (59).

Therapeutic role of alkaloids in diabetes

One mechanism of action of alkaloids in T₂D therapy includes 5'-Adenosine monophosphate-activated protein kinase (AMPK) activation. AMPK has a vital role in various physiological and pathological conditions including cell metabolism, stimulation of glucose uptake, modulation of insulin production and the innate and adaptive immune response to infections (60, 61). In the 3T3-L1 cell line, it was shown that Berberine caused AMPK phosphorylation which remained constant for 16 h (62). Berberine may also act as an α -glucosidase inhibitor by berberine ability to lower blood insulin level via enhancing insulin sensitivity. However, in patients with poor β -cell function, berberine may improve insulin secretion through stimulating of exhausting islets (63). Boldine, an aporphine alkaloid can be extracted from the medicinal plant *Peumus boldus* had a protective role against oxidative damage caused by STZ in the pancreas, kidney and liver of a diabetic rat model (64). Study by Bangning and his colleagues reported that boldine is able to modulate the expression of adiponectin and its regulators in 3T3-L1 cells and has potential therapeutic benefits in obesity-related cardiovascular disorder (65). Betanin, a natural pigment and chromoalkaloid of beetroot, has shown significant biological effects of antioxidants, anti-inflammatory and anticarcinogenic activities (66). In streptozotocin (STZ) – nicotinamide (NA) induced diabetic rats, betanin significantly restored the levels of carbohydrate metabolic key enzymes to near normal by increasing the activity of glucokinase and pyruvate kinase and decreasing of gluconeogenic enzymes activity. Also, betanin increased insulin immunoreactive β -cells in the pancreas of diabetic rats which has beneficial effect in glucose homeostasis (67)

The risk of using pyrrolizidine alkaloids as a dietary supplement

Alkaloids have important therapeutic roles in numerous disorders as we showed previously. However, several studies have reported a risk for the use of pyrrolizidine alkaloids. Pyrrolizidine alkaloids (PA) are a group of natural alkaloids based on the structure of pyrrolizidine and are widely distributed in plants throughout the world. They are frequently found in plant species distributed for human consumption, especially 1,2-unsaturated PAs which are a concern because they are considered genotoxic carcinogens (68). Risk Assessment (BfR) in Germany reported that botanical preparations such as (herbal) teas and plant food supplements (PFS) have PA contamination but in most cases these levels are insufficient to cause acute poisoning (69). BfR results obtained by the analysis of seven types of herbal drugs (41 samples) and 11 types of (herbal) teas (282 samples). The results showed that (herbal) teas can contain significant levels of PAs of up to 5647 $\mu\text{g}/\text{kg}$ dry material, while in herbal drugs a total PA level could reach up to 3099 $\mu\text{g}/\text{kg}$ (70). Frequent consumption of PA can increase the current and future risks of acute poisoning while contributing to the probability of chronic disease (71). The expert opinion to avoid disease influenced by PA is to avoid PA contamination during farming and productions, by selecting the correct herb, at the right time with the right technique for harvesting, in addition to weed control which remains a substantial challenge in industrial farming (72).

Author Contribution Statement:

Conceptualization, W.H.N; writing-original draft preparation, W.H.N and H.S.S.A; resources, A.R. review and editing, W.H.N final draft editing.

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