1. Introduction

1.1 Herbal medicines

Herbal medicines are naturally occurring, plant-derived substances that are used to treat illnesses within local or regional healing practices. These products are complex mixtures of organic chemicals that may come from any raw or processed part of a plant. Herbal medicine has its roots in every culture around the world. There are many other systems of traditional medicine, and practices of each are affected by social behaviour, environment and geographic location, but all these systems agree on a holistic approach to life. Herbal medicine has its origins in ancient cultures. It involves the medicinal use of plants to treat disease and enhance general health and wellbeing. Herbal medicine, also known as herbalism or botanical medicine, is a medical system relied on the use of plants or plant extracts that may be eaten or applied to the skin. Since ancient times, herbal medicine has been used by many different cultures throughout the world for many treatments like malaria, warts, bowel disorders, heart conditions and chronic pain, come from pharmacists and doctors learning about folk knowledge. [1]

Medicinal plants provide a host of chemical compounds, which have been optimized on the basis of their Pharmacological activities. Chemical compounds present in medicinal plants have shown great promise in the management of various inflammatory disorders and have continued to serve as alternative and complementary therapies.

1.2 Inflammation

Inflammation is a localized physical condition in which the inflamed part of the body develops swelling, redness, pain, etc. as a result of an infection or injury. Infections, wounds, and tissue damages cannot heal without an inflammatory response. This response is mediated by two main components of the host's defense mechanisms: innate and adaptive immune response. The innate immune response is the primary host response to any foreign material which then is acted upon by granulocytes, phagocytes and other cells which are a part of the adaptive immune response. The adaptive immunity is characterized by specificity and helps in the elimination of pathogens in the later phase as well as the generation of immunological memory. However, sometimes the inflammatory response persists longer than necessary which causes more harm than benefit. Inflammation is also now thought to contribute to a variety of diseases that are metabolic, degenerative or genetic e.g. diabetes, Alzheimer disease and cancer. [2]

1.3 Types of inflammation

1.3.1 Acute inflammation- Acute inflammation usually has becoming within minutes or at most hours after tissue injury and may be characterized by the classical symptoms of redness, heat, oedema. It is a short-term process. It is characterized by the exudation of fluids and plasma proteins and the migration of leukocytes, most importantly neutrophils into the injured area. This acute inflammatory response is useful to the defense mechanism aimed at killing of bacteria, virus and parasites while still facilitating wound repairs.[3]

a) Causes of acute inflammation:

Acute inflammation can be caused by immediate reasons such as a knee bruise (injuries), or a sprained ankle. The blood vessels will dilate, leading to redness and swelling, which usually subsides with time and medication/treatment for the underlying cause.

Other causes of acute inflammation include:

- **Diseases** – Medical conditions such as acute bronchitis, tonsillitis, etc can induce an inflammatory response in the body.
- **UV rays** – Ultraviolet rays cause an acute inflammatory response in the skin by inducing the release of proinflammatory cytokines.
- **Inflammatory foods** – Processed meat, refined carbohydrates, vegetables, seed oils, etc can induce inflammation in a region depending on the underlying condition.
- **Exposure to chemicals** – Chemicals such as benzene, ketones, halocarbons, etc can leave the exposed regions in an inflammatory state.
- **Smoking** – Nicotine present in the cigarettes activates some white blood cells called neutrophils that cause inflammation in the body. [4]
- **Exposure to external invaders** – Inflammation is the body's response to an injury or a pathogen or infection.
- **Sleep deprivation** – Loss of even a single night's sleep can lead to a cellular pathway that causes inflammatory responses in the body tissues.[5]

b) Outcomes of acute inflammation

Typically, 3 possible outcomes are:

- **Complete resolution**: Ideal outcome. Usually only if injury is limited or short-lived with little tissue destruction, allowing removal of cellular debris and microbes by macrophages, resorption of oedema fluid and regeneration of damaged cells.

- **Scarring / fibrosis:** Healing by connective tissue replacement (organization). Occurs after substantial tissue destruction, the damaged tissue cannot regenerate or fibrinous exudate cannot be cleared adequately.
- **Progression to chronic inflammation:** Occurs when the acute inflammatory response cannot be resolved due to persistence of injurious agent or other interference with the normal healing process.

1.3.2 Chronic inflammation - Chronic inflammation is of a more prolonged duration and histologically by the presence of lymphocytes and macrophages, resulting in fibrosis and tissue necrosis. The chronic inflammation increases the development of the degenerative disorders such as rheumatoid arthritis, atherosclerosis, cardiovascular disorders, Alzheimer, asthma, acquired immunodeficiency disorder (AIDS), cancer, congestive heart failure, multiple sclerosis, diabetes, infections, gout, IBD-inflammatory bowel disease, aging and other neurodegenerative CNS depression, Chronic inflammation also has been implicated as part of the cause of the muscle loss that occurs with aging. All of which are associated with immunopathological that seems to have a key role in the onset of the condition.[6]

Chronic inflammation is not always a progression of acute inflammation. It can manifest as a standalone response too. As an example, medical conditions such as arthritis and tuberculosis can cause chronic inflammation without the person necessarily having a history of acute inflammation.[7]

a) Causes of chronic inflammation:

- **Chronic stress** – Studies have shown that chronic stress can alter the gene activity of immune cells, causing them to be ready to fight trauma even when there isn't any.
- **Alcoholism** – Overconsumption of alcohol on a regular basis led to the overproduction of reactive oxygen species, known for their ability to stimulate a key inflammation transcription factor.[8]
- **Obesity** – Obesity can cause low-grade chronic inflammation. Fat is basically adipose tissue, and this tissue stores energy in the form of triglycerides, and produces molecules called adipocytokines which induce a chronic inflammatory response in the body.[9]

1.4 Signs and symptoms of inflammation

- **Pain**: This may occur continuously or only when a person touches the affected area.
- **Redness**: This happens because of a higher blood supplement to the capillaries in the area.
- **Loss of function**: There may be difficulty moving a joint, breathing, sensing smell, and so on.
- **Swelling**: A condition called edema can develop if fluid builds up.
- **Heat**: Increased blood flow may leave the affected area warm to the touch.[10]

Symptoms

- **Body pain-** Body pain is a result of over-sensitized nerve fibres. Prostaglandin receptors regulate the pain. Body pain is generally reduced by inhibiting the synthesis of prostaglandin.
- **Relentless fatigue and sleeplessness** – It have been studied that cytokines cause fatigue and insomnia during inflammation. Cytokines are secreted by the immune system during an inflammatory response. Biological agents that suppress cytokines are known to reduce fatigue and insomnia.
- **Anxiety, mood swings, and depression** – Although inflammation does not have a direct correlation with depression, the onset of inflammation and associated physiological changes can cause depression. Medication administered to counter chronic inflammation, specifically, cytokine inhibitors have been studied to affect cortical and subcortical areas of the brain.
- **Weight increase** – Due to a reduction in metabolic rate, obesity can manifest in those with chronic inflammation.
- **Feverishness** – It includes chills, feeling of fatigue, energy loss. There is a rise in temperature in the entire body resulting from the site of infection.
- **Headache** – Sinus cavities become inflamed leading to headaches.
- **Decreased appetite** – It is the body's response to prevent the virus from growing further.[11]

1.5 Acute Vs. Chronic inflammation.

Table 1.1. Acute Vs. Chronic inflammation [11]

Characteristics	Acute	Chronic
Cause	Harmful pathogens or tissue injury.	Pathogens that the body cannot break down, including some types of viruses, foreign bodies that remain in the system, or overactive immune responses.
Onset	Rapid.	Slow.
Duration	A few days.	From months to years.
Outcomes	Inflammation improves, or an abscess develops or becomes chronic.	Tissue death, thickening, and scarring of connective tissue.
Magnitude	High-grade	Low-grade
Age-related	No	Yes
Biomarkers	IL-6, TNF-α, IL-1β, CRP	Silent—no canonical standard biomarkers
Trigger	PAMPs (infection), DAMPs (cellular stress, trauma)	DAMPs (‘exposome’, metabolic dysfunction, tissue damage)
Cellular infiltrate	Neutrophils (associated with tissue oedema due to fluid and plasma protein exudates)	Monocytes/macrophages and lymphocytes
Tissue injury	Usually, self-limited	More destruction and scarring (fibrosis)

DAMP- Damage-associated molecular pattern;

PAMP- Pathogen-associated molecular pattern.

1.6 Inflammatory cascade

The inflammatory process is a combination of many pathways like a synthesis of prostaglandin, interleukin or other chemo toxin, adhesive protein receptor action, platelet-activating factors. Inflammation involves localized rise in leukocyte number and many complex mediators. Prostaglandins are universal substances which indicate and modulate the tissue responses during inflammation. The inflammation is either acute or chronic and occurs in three distinct phases. Inflammation starts from an increased vascular permeability, infiltration of leukocytes, followed by granuloma formation and tissue repair. Arachidonic acid metabolites, adhesion molecules, cytokines, chemokines, and platelet-activating factor cause release of other mediators and initiates chemotaxis. The microbial products and host proteins like complement proteins, kinins, and coagulation system activates the production of inflammatory mediators. Various inflammatory mediators like complement proteins and kinins originate from plasma, whereas histamine, prostaglandins and cytokines originate from cells. Arachidonic acid metabolites like leukotrienes (LTs), prostaglandins (PGs), and 12-Hydroxyeicosatetraenoic acid (12-HETE) are actively involved in the development of inflammatory diseases, like asthma, arthritis, and cancer. Inflammation is a result of activated cellular elements and the existence of various biochemical mediators like cytokines (e.g., Interleukin-1, TNF-α), Kinases (p38 kinase, JNKs, MAP kinase), transcription factors and matrix metalloproteinases (MMPs) The inflammatory cascade is shown in Figure 1.1(A, B) [12,13,14]

The predominant inflammatory cell type in acute inflammation depends on the timing and type of stimulus:

- **6-24 hrs:** Neutrophils. Early responder as they are more numerous than other leukocytes in the blood, respond more rapidly to chemokines and may attach more firmly to endothelial cells. However, they are short-lived, with most in extravascular tissue undergoing apoptosis in a few days.
- **24-48 hrs:** Monocytes / macrophages. Survive longer than neutrophils and can also proliferate in tissues, and therefore eventually dominates in prolonged inflammation.
- **Exceptions to the above depend on type of stimulus**: lymphocytes predominate for viral infections, eosinophils for parasites and allergic reactions, etc.

Table 1.2 Mediators that regulate the acute inflammatory response [15]

Mediator class	Pro-inflammatory	Anti-inflammatory
Amines	Histamine, bradykinin	Adrenaline, noradrenaline
Lipid mediators	PGE2, PGI2, LTB4, LTC4	PGJ2, PGA1/2, lipoxins
Complement	C3a, C5a	C1q receptor
Cyclic nucleotides	cGMP	cAMP
Adhesion molecules	E-selectin, P-selectin, ICAM1, VCAM1	αvβ3 integrin, TSP receptor, PS receptor
Cytokines	TNF-α, IL-1β, IL-6, IL-4	TGF-β1, IL-10
Chemokines	IL-8 (CCL8), GRO/KC, MIP1α (CCL3), MCP1 (CCL2)	-
Steroid hormones	-	Glucocorticoids

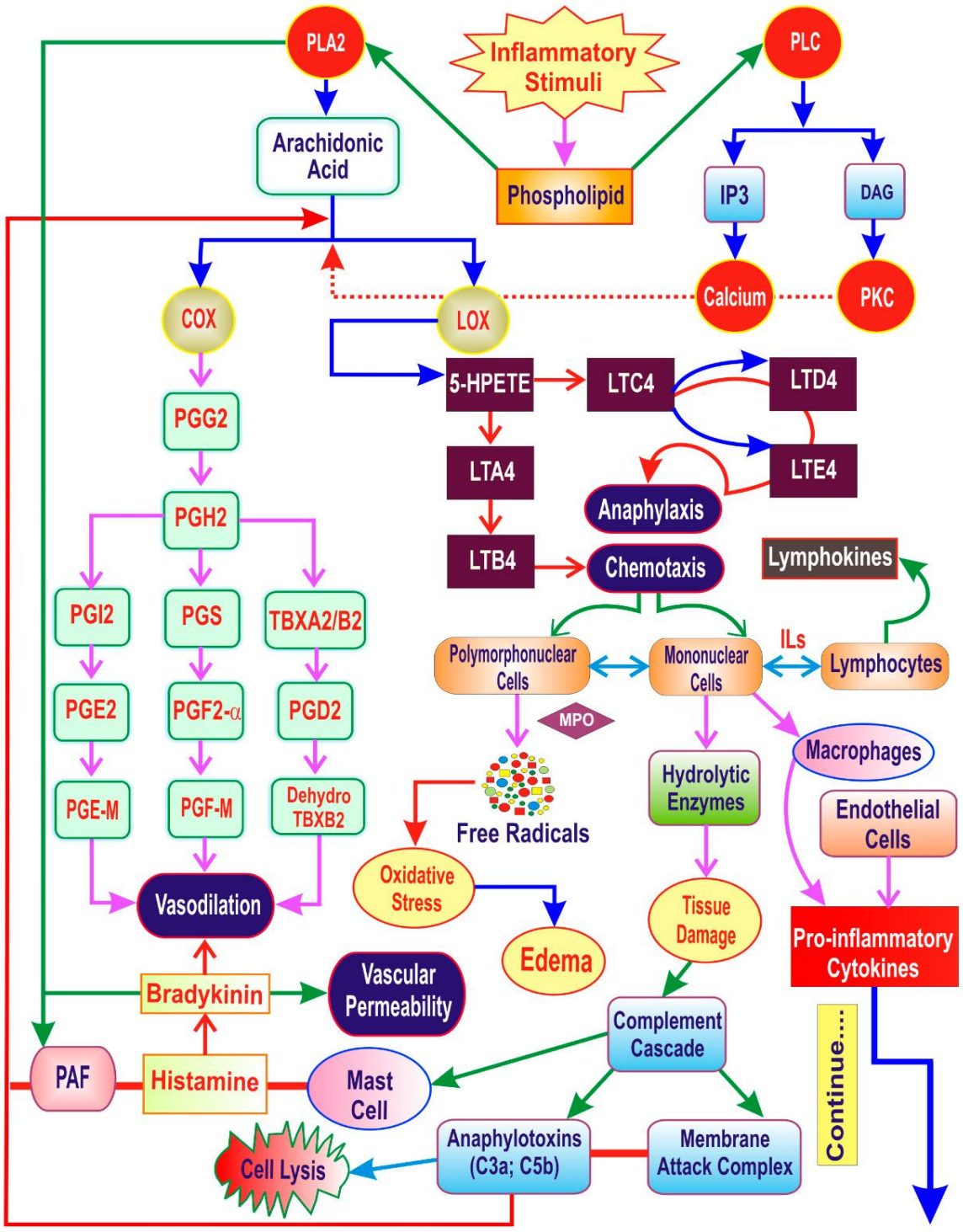

Figure 1.1. (A) The inflammatory cascade [25]

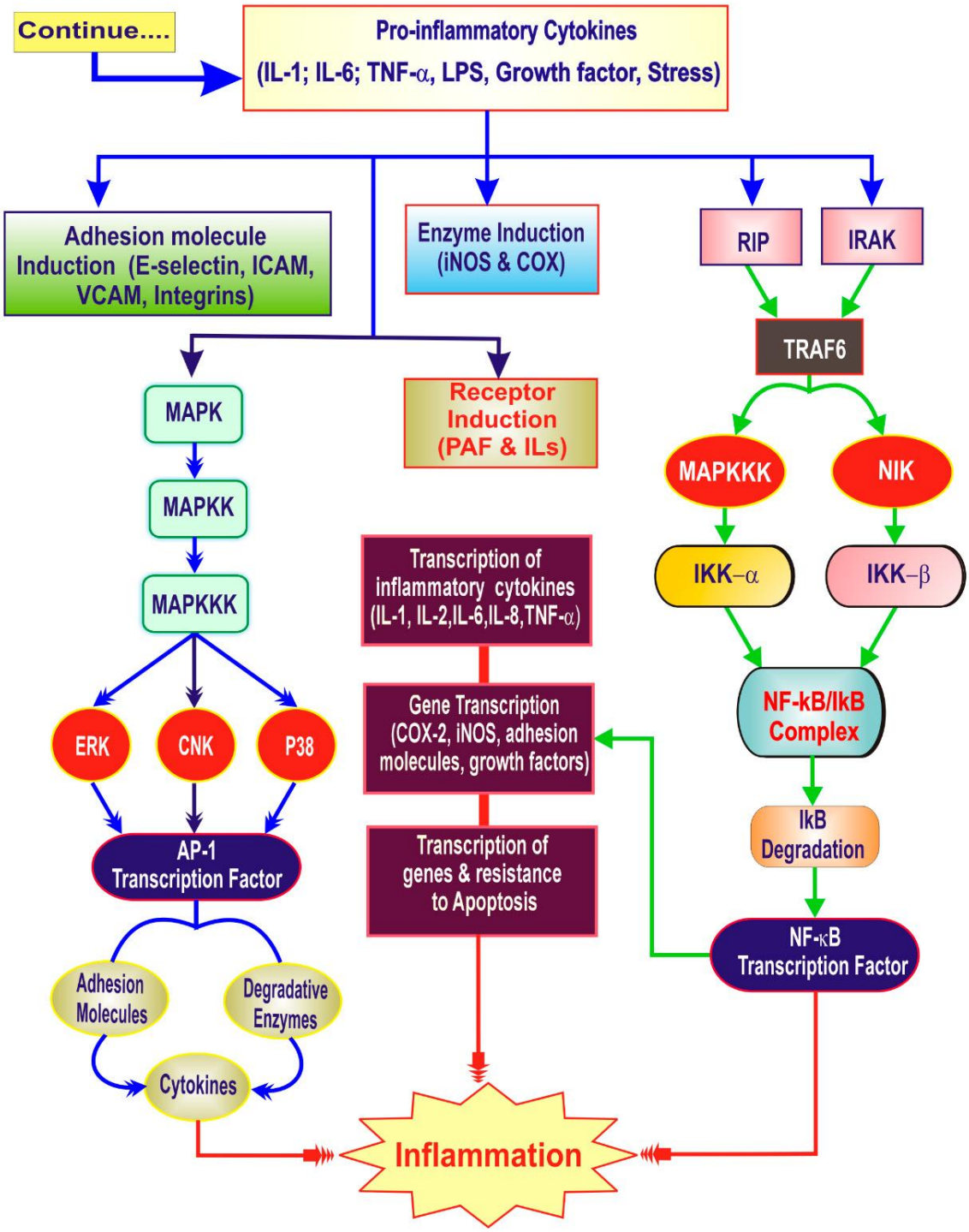

Figure 1.1 (B) [25]The inflammatory cascade; (cAMP- Cyclic adenosine 3,5 monophosphate,IL- Interleukin, cGMP- Cyclic guanosine 3,5 monophosphate, LT- Leukotriene, ICAM1- Intercellular adhesion molecule 1, PG- Prostaglandin, MCP1- Monocyte chemotactic protein 1, PS- Phosphatidylserine, MIP1α- Macrophage inflammatory protein 1α, TNF-Tumour-

necrosis factor, TGF-β1-Transforming growth factor-β1, TSP-Thrombospondin, VCAM1-Vascular cell adhesion molecule 1.)

1.7 Chemical Anti-Inflammatory Drugs

Chemical Anti-Inflammatory Drugs are usually synthetic drugs that prevent inflammatory process by hormonal action, inhibiting inflammatory enzymes, proteins, and factors or favouring anti-inflammatory response. [16] They belong to two different classes based on the presence and absence of steroidal moieties. Accordingly, they can be steroidal anti-inflammatory drugs and Non-Steroidal Anti-Inflammatory Drugs. (NSAIDs) [17]

1.7.1 Steroidal Anti-Inflammatory Drugs (SAIDs)

SAIDs were the first to be applied against inflammatory conditions and are fast and potent in action. They contain steroid hormones, corticosteroids or glucocorticoids (GCs). GCs are a class of corticosteroids, which are a class of steroid hormones (dexamethasone, prednisolone). Glucocorticoids are corticosteroids that are having anti-inflammatory, immunosuppressive, metabolic, and developmental, arousal and cognition, body fluid homeostasis effects. [18] They are used in physiological replacement, therapeutic immunosuppression, anti-inflammatory, hyperaldosteronism, resistance, heart failure. However, there are many side effects and limitations associated with steroidal anti-inflammatory drugs. The main side effects and limitations are abortion, immunodeficiency, weight gain, hormonal disturbances, dependency, withdrawal complications, cost and availability. [19]

1.7.2 Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

NSAIDs were developed to overcome side effects and limitations of steroidal anti-inflammatory drugs. They have proven beneficial in many attributes and are quite effective. Different classes of NSAIDS are based on chemical derivatives and mechanism of action. [20] Chemically, they can be salicylate derivatives (aspirin, sodium salicylate & diflunisal), propionic acid derivatives (ibuprofen, ketoprofen, naproxen), aryl acetic acid derivatives (diclofenac, ketorolac), indole derivatives (indomethacin, sulindac), alkanones (nabumetone), oxicams (piroxicam, tenoxicam, meloxicam), anthranilic acid derivatives (fenamates) (mefenamic acid and flufenamic acid), pyrazolone derivatives (phenylbutazone, oxyphenbutazone, azapropazone (apazone) and dipyrone (novalgine), and aniline derivatives (analgesic only) (paracetamol).[21] Based on the mechanism of action they can be non-selective irreversible COX inhibitors, non-selective reversible COX inhibitors, preferential COX 2

inhibitors (meloxicam, etodolac, nabumetone), selective COX 2 inhibitors (celecoxib, etoricoxib, rofecoxib, valdecoxib) and COX 3 inhibitor (PCM) [22,23]

1.8 Importance of Herbal medicines

Natural products significantly differ from synthetic drugs by the frequency of different atoms, radicals and spatial configuration. Modern medicine has only recently recognized the rapid development of resistance by pathogens and cancer cells to single-agent drugs, leading to the use of complex drug cocktails to manage or delay such resistance. Plants, however, have employed a similar strategy since early in their evolutionary history. By utilizing combinations of pleiotropic, multi-targeted molecules, plants have evolved to use phytochemical complexes that interact in complementary ways to address various biological challenges. This natural approach underscores the sophistication of plant-based strategies in managing complex biological processes and highlights the potential of integrating such multi-faceted mechanisms into therapeutic practices. The mechanisms of synergism among the compounds present in a single herbal extract are mainly related to two factors: the simultaneous solubility of a group of substances with different polarities, and the multiplicity of targets that these substances can act on, including enzymes, receptors, ion channels, transport proteins, antibodies, and many others.

1.9 Limitations of herbal medicines

Phytomedicine is not well accepted by the medical community and pharmaceutical industry because of a belief that it lacks safety and efficacy validation and regulations, as well as concerns on poor standardization and quality control, mistakes in nomenclature, difficulties in identifying active ingredients and determining their complex modes of action.

1.10 References

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