



# Solving the puzzle: What is behind our forefathers' anti-inflammatory remedies?

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## ABSTRACT

Inflammation is a ubiquitous host response in charge of restoring normal tissue structure and function but is a double-edged sword, as the uncontrolled or excessive process can lead to the injury of host cells, chronic inflammation, chronic diseases, and also neoplastic transformation. Throughout history, a wide range of species has been claimed to have anti-inflammatory effects worldwide. Among them, *Angelica sinensis*, *Tropeolum majus*, *Castilleja tenuiflora*, *Biophytum umbroculum*, to name just a few, have attracted the scientific and general public attention in the last years. Efforts have been made to assess their relevance through a scientific method. However, inflammation is a complex interdependent process, and phytomedicines are complex mixtures of compounds with multiple mechanisms of biological actions, which restricts systematic explanation. For this purpose, the omics techniques could prove extremely useful. They provide tools for interpreting and integrating results from both the classical medical tradition and modern science. As a result, the concept of network pharmacology applied to phytomedicines emerged. All of this is a step toward personalized therapy.

**KEY WORDS:** Inflammation, omics applied to phytomedicine, rational phytotherapy, traditional medicinal system

## INTRODUCTION

Inflammation, an important component of innate immunity, is a ubiquitous host response to foreign physical and/or chemical challenges, invading pathogens [1] or tissue injury, ultimately isolating the source of disturbance, eradicating infection, and restoring normal tissue structure and function (homeostasis) [2]. It is a complex process that is frequently associated with pain and involves several events such as vasodilatation, plasma extravasations, cellular migration (neutrophils) and in some cases, the activation of coagulation cascades [3]. Its

characteristic signs include redness, heat, tumor, pain, and loss of function [4]. On the one hand, inflammation is a host defense mechanism meant to eliminate invading pathogens and initiate the healing process. On the other hand, inflammation is a double-edged sword, as the uncontrolled or excessive production of inflammatory products can lead to the injury of host cells, chronic inflammation, chronic diseases, and also neoplastic transformation [5]. Despite progress within medical research during the past decades, the treatment of many serious diseases remains problematic, and chronic inflammatory diseases remain one of the world's major health problems [6,7].

Nowadays, we know that inflammation is a global term that encompasses a multitude of processes that can vary widely in spite of the interdependency and the existence of overlapping signaling pathways. Not only is chronic inflammation different from acute, but inflammatory activity also differs depending on the disease, even if the classical signs and symptoms are similar. For example, the inflammation involved in dry eye disease is accompanied by a specific profile that is wholly separate from inflammation in Crohn's disease sustained, among others, on diverse defects on regulatory mechanisms [8,9]. For this reason, it makes sense that patients with different illnesses do not receive the same prescription for inflammation management. Targeted therapies could increase treatment success [10], reduce toxicity and adverse events including overdose, over the duration, tolerance, dependence/addiction, hypersensitivity, and mid- and long-term toxic effects [11].

Inflammation is not something new. For a long time, different cultures around the world have used herbs and spices - or their formulations - to treat inflammatory disorders and related diseases more or less gracefully [12]. In the course of history, an extraordinarily large number of plant species have been claimed worldwide to possess anti-inflammatory abilities. Some of them have demonstrated their ethnopharmacological relevance and are the main medical treatment for two-thirds of the world population, which is due to the limited availability and affordability of the standard pharmaceutical medicines used in developed countries [13]. The World Health Organization estimates that 80% of people in the developing countries use traditional medicine as primary health care [14].

In light of the above, when referring to the pharmacological anti-inflammatory activity of each species, there is a need for specificity. What is the principle role that each species plays in reducing inflammation? With regard to anti-aggregation, for example, a concrete compound or group of compounds have been described for the extract of *Ginkgo biloba*; a precise mechanism of action and a specific posology have been described to assess its therapeutic effect and reduce adverse events or achieve synergy [15], but the explanation is not always easy. In the case of the anti-inflammatory action, very diverse pathways could achieve it, and the molecular mechanism underlying it sometimes remains unclear. Anti-inflammatory natural products chemistry is complex and the structure diverse. It includes fatty acids, for example,  $\gamma$ -linolenic acid in *Oenothera biennis*, phenylpropenes such as cinnamaldehyde in *Cinnamomum zeylanicum*, or phenolic glycosides as salicin in *Salix purpurea*, to name just a few. In recent years, the concept of network pharmacology, in which low doses of multiple drugs are used to treat diseases, has been developed to understand complex diseases as networks, for which the most efficient treatment is multi-targeted [16]. This depth of knowledge would enable the development of potential new agents, particularly in the inflammation field.

Here, four different actions generally investigated when anti-inflammatory activity is assessed have been selected, and a number of popular species used to treat inflammatory ailments by people in totally different cultural backgrounds (China,

America, Africa, Europe, India, and Australia) have also been chosen [Table 1]. Ethnopharmacological relevance (cultural meaning, bioprospective, and/or standardized use), state of science (e.g., scientific rigor, innovation, novelty, or preclinical *in vivo* studies), scientific and social impact of publications under them and use in differentiated geographical locations have been the main parameters chosen to design this research. In most cases, only earlier studies on ethnobotany, phytochemistry, and the pharmacological effects on these species have been reported to date, but there is enough information to form an initial idea of possible trends, therapeutic potentials, possibilities for future research and, no less important, to understand inflammation as an intricate process that involves a wide range of pathophysiological disorders, cells and signaling pathways. This does not imply that rationality does not must guide all decisions when phytotherapy is selected as a health resource and phytomedicines designed and prescribed.

## METHODOLOGY

Information about the anti-inflammatory medicinal plants presented here was obtained from published papers and texts on ethnobotanical studies. The selection of relevant data was made by systematically searching the electronic scientific databases including PubMed, Scopus, SciFinder, and the Web of Science and other web machineries such as Google and Google Scholar. Textbooks, theses, Government survey reports, unpublished materials as well as articles published in peer-reviewed journals were also used for the compilation of data. References were also searched to retrieve the related literature. Some plant name databases including "The Plant List" ([www.theplantlist.org](http://www.theplantlist.org)) and "Kew Royal Botanic Gardens" ([mpns.kew.org](http://mpns.kew.org)) were used to validate the scientific name of the plant.

## RESULTS

### Regulation of Nuclear Factor-kappa B (NF- $\kappa$ B) Pathway [Figures 1 and 2]

The expression of various pro-inflammatory cytokines and chemokines such as tumor necrosis factor (TNF- $\alpha$ ) and interleukin (IL-1) (the main cytokines responsible for neutrophil recruitment to the inflammatory site, activation, modulation, and the trafficking of AMPA receptors in models of inflammatory pain [17]) as well as IL-6, IL-12p35, macrophage (MPH) inflammatory protein-2 (MIP-2), the C-X-C motif chemokine 10 (CXCL-10 or IP-10), or the C-C motif chemokine ligand 3 (CCL-3 or MIP-1- $\alpha$ ) [18] are induced by NF- $\kappa$ B activation [19]. NF- $\kappa$ B is an important transcription factor, and it is essential for inducing the expression of a wide variety of cellular genes that are related to the pathophysiological process of inflammation in mammalian cells. Five members constitute the NF- $\kappa$ B family: (1) p65 (or RelA), (2) RelB, (3) c-Rel, (4) the p50/p105 complex (or NF- $\kappa$ B 1), and (5) the p52/p100 complex (or NF- $\kappa$ B 2) [18]. NF- $\kappa$ B exists within the cytoplasm in an inactive form that is associated with a set of regulatory proteins called I- $\kappa$ Bs, including I- $\kappa$ B $\alpha$ , and I- $\kappa$ B $\zeta$ . Stimulation leads to the phosphorylation of I- $\kappa$ B

**Table 1: Species used on inflammatory ailments. The origin, the principal mechanism involved and the ethnopharmacological use are collected**

Species used on inflammatory ailments				
Native to	Mechanism involved	Species	Ethnopharmacological use	Bibliographical reference
China	1. Nuclear factor kappa- $\beta$	<i>Angelica sinensis</i>	Blood stasis, analgesia, rheumatism and	[27]
	2. MPH and mononuclears	<i>Magnolia</i> spp.	bruises	[52]
	3. COX and LOX inhibition	<i>Tripterygium wilfordii</i>	Allergic rhinitis and sinusitis	[120]
	4. Toll-like receptors and inflammasomes	<i>Zanthoxylum myriacanthum</i> var. <i>pubescens</i>	Neuralgia, dropsy, and gout Gastrointestinal disorders, parasite invasion, and centipede bites	[71]
America	1. Nuclear factor kappa- $\beta$	<i>Polygala molluginifolia</i>	Pain and inflammation	[31]
	2. MPH and mononuclears	<i>Critonia aromatisans</i>	Inflammation and arthritis	[4]
	3. COX and LOX inhibition	<i>Castilleja tenuiflora</i>	Coughs, dysentery, nerves, nausea, vomiting	[96]
	4. Toll-like receptors and inflammasomes	<i>Polygala sabulosa</i>	Tonic remedy, topic an esthetic and expectorant	[72]
Africa	1. Nuclear factor kappa- $\beta$	<i>Harpagophytum procumbens</i>	Pain and osteoarthritis	[37]
	2. MPH and mononuclears	<i>Biophytum umbraculum</i>	Dysregulated inflammation, conjunctivitis,	[59]
	3. COX and LOX inhibition	<i>Kigelia africana</i>	vaginitis	[104]
	4. Toll-like receptors and inflammasomes	<i>Xanthium strumarium</i>	Articular rheumatism, waist pain, wounds Rheumatism, constipation, diarrhea	[23]
Europe and India	1. Nuclear factor kappa- $\beta$	<i>Calea urticifolia</i>	Gastric ulcers, diabetes, and inflammation	[40]
	2. MPH and mononuclears	<i>Zataria bracteata</i>	Antiseptic, analgesic, carminative,	[61]
	3. COX and LOX inhibition	<i>Tropaeolum majus</i>	anthelmintic	[107]
	4. Toll-like receptors and inflammasomes	<i>Origanum vulgare</i>	Cardiovascular disorders (antihypertensive and diuretic) Convulsive coughs, colds, skin diseases	[81]
Australia	1. Nuclear factor kappa- $\beta$	<i>Salvia plebeia</i>	Hepatitis, cold, tumors, and inflammation	[48]
	2. MPH and mononuclears	<i>Carpobrotus rossii</i>	Upper respiratory tract and throat infections	[66]
	3. COX and LOX inhibition	<i>Clematis pickeringii</i>	Headaches, colds, and muscular pain	[112]
	4. Toll-like receptors and inflammasomes	<i>Vitex trifolia</i>	Fever, pain, rheumatism and sprained joints	[86]

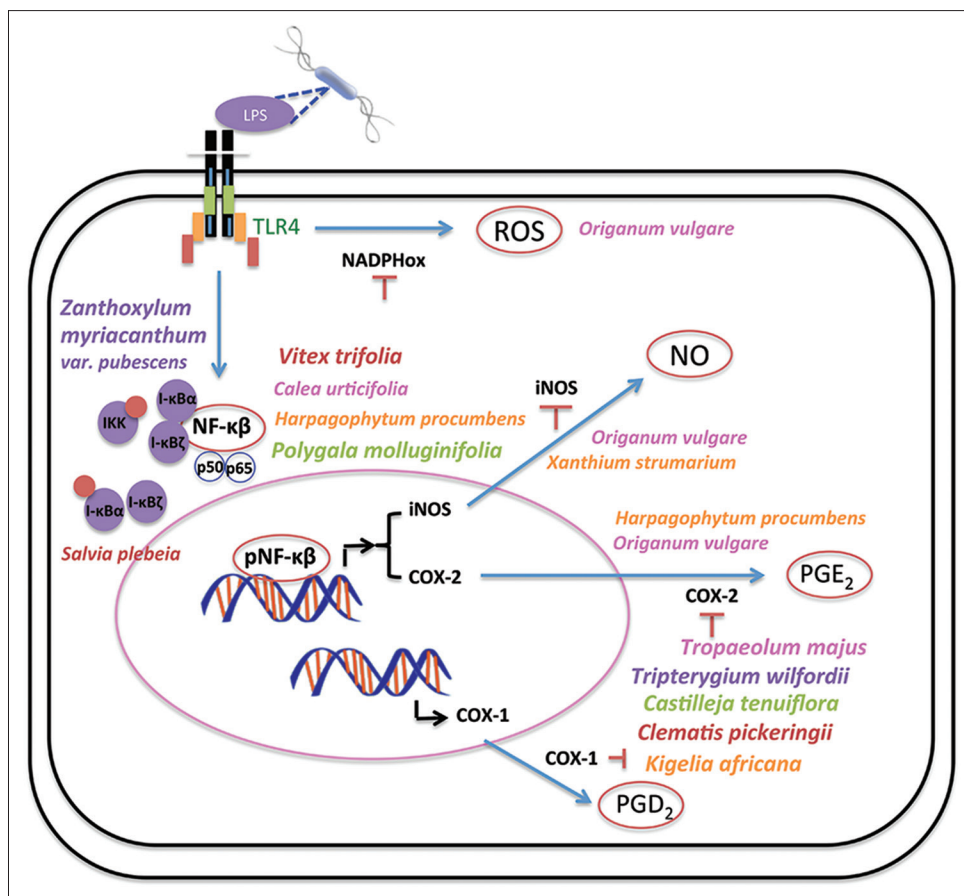
*A. sinensis*: *Angelica sinensis*, *T. wilfordii*: *Tripterygium wilfordii*, *Z. myriacanthum*: *Zanthoxylum myriacanthum*, *P. molluginifolia*: *Polygala molluginifolia*, *C. aromatisans*: *Critonia aromatisans*, *C. tenuiflora*: *Castilleja tenuiflora*, *P. sabulosa*: *Polygala sabulosa*, *H. procumbens*: *Harpagophytum procumbens*, *B. umbraculum*: *Biophytum umbraculum*, *K. Africana*: *Kigelia Africana*, *X. strumarium*: *Xanthium strumarium*, *C. urticifolia*: *Calea urticifolia*, *Z. bracteata*: *Zataria bracteata*, *T. majus*: *Tropaeolum majus*, *O. vulgare*: *Origanum vulgare*, *S. plebeian*: *Salvia plebeian*, *C. rossii*: *Carpobrotus rossii*, *C. pickeringii*: *Clematis pickeringii*, *V. trifolia*: *Vitex trifolia*, MPH: Macrophage, COX: Cyclooxygenases

by I- $\kappa$ B kinase (IKK), I- $\kappa$ B $\alpha$  proteasomal degradation [20] and the nuclear release and accumulation of p65, which allows the NF- $\kappa$ B dimers translocate to the nucleus [21]. Microtubule-associated protein (MAP) and AGC kinases are also important factors in the signal transduction [22]. The phosphorylation of ERK 1/2, JNK, and p38 MAPK activates a series of transcription factors such as AP-1, CREB, c-Jun, and signal transducer and activator of transcription 1 (STAT1), which result in NF- $\kappa$ B activation [23]. The overexpression of the NF- $\kappa$ B pathway leads to the formation, among others, of IL-1 $\beta$  and prostaglandin E (PGE<sub>2</sub>) [24] and the induction of cyclooxygenases-2 (COX-2) and inducible nitric oxide synthase (i-NOS) [25].

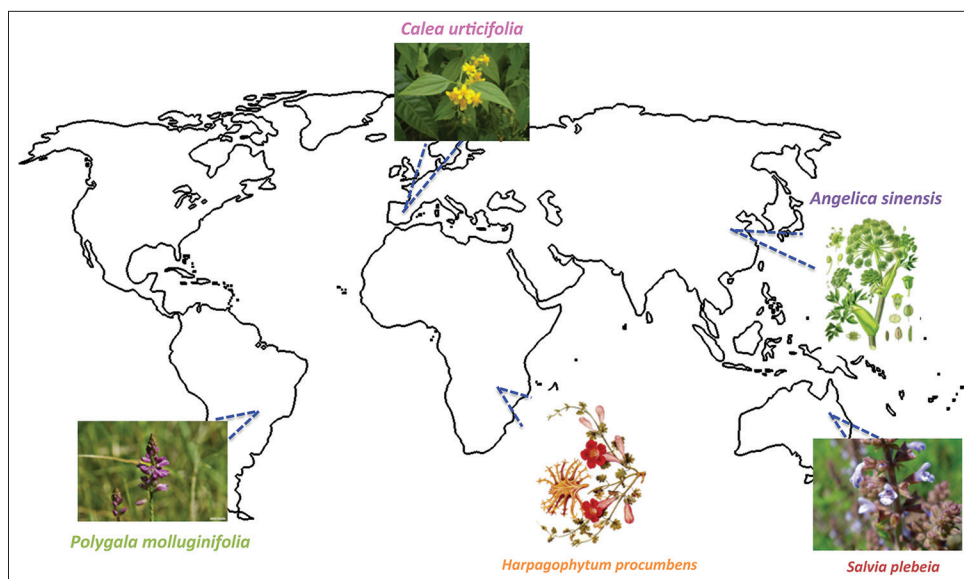
#### A. China

The prescreening of 22 commonly used Chinese herbs by NF- $\kappa$ B-dependent activity showed that the ethyl acetate (EtOAc) fraction of *Angelica sinensis* ("Dang Gui" in China, Apiaceae) root, *Morus alba* (Moraceae) root and bark and *Andrographis paniculata* (Acanthaceae) aerial part extract (both 10 g of drug in 300 mL of 95% ethanol at 50°C for 3 h, twice) all suppressed NF- $\kappa$ B luciferase activity and decreased NO and PGE<sub>2</sub> production in lipopolysaccharide (LPS)/interferon (IFN)- $\gamma$ -stimulated peritoneal MPHs [26]. *A. sinensis* root extract achieved

the highest NF- $\kappa$ B luciferase activity inhibition. This root herb is commonly used in traditional Chinese medicine (TCM) and as a dietary supplement in women's care in Europe [27]. It has been called "female ginseng" for its use in the treatment of various gynecological conditions that are generally not easily treated with conventional therapies [27]. The Pharmacopoeia of the People's Republic of China [28] records that it can be applied to treat blood stasis, analgesia, rheumatism, and bruises, and it can also be used as an anti-inflammatory herb. The most commonly used prescriptions containing *A. sinensis* are formulated in decoctions, pastes, vine extracts, and tablets [29]. The EtOAc extract from *A. sinensis* root has been widely evaluated for its ability to modulate NF- $\kappa$ B transactivation activity in an NF- $\kappa$ B-promoted luciferase reporter gene assay and for its *in vivo* anti-inflammatory effects in a murine model of LPS-induced endotoxic shock [19]. Two major compounds of *A. sinensis* - ferulic acid and Z-ligustilide - do possess anti-inflammatory properties. This last, a highly lipophilic compound, has been shown to have a significant anti-inflammatory effect related to the inhibition of the TNF- $\alpha$ -activated NF- $\kappa$ B signaling pathway. Metabolomics-based on gas chromatography and mass spectrometry have been employed to investigate, discriminate and classify the anti-inflammatory effects of *A. sinensis* root and its different



**Figure 1:** Regulation of the NF- $\kappa$ B pathway. *Polygala molluginifolia*, *Harpagophytum procumbens*, *Vitex trifolia* and *Calea urticifolia* inhibit p50 and/or p65 phosphorylation and NF- $\kappa$ B translocation into the nucleus; *Salvia plebeia* suppresses I $\kappa$ B $\alpha$  degradation, which hinders nuclear translocation of NF- $\kappa$ B; and *Zanthoxylum myriacanthum* var. *pubescens* blocks the downstream IKK and I- $\kappa$ B phosphorylation. *Xanthium strumarium* diminishes NO and PGE<sub>2</sub> levels. *Tripterygium wilfordii* and *Clematis pickeringii* inhibit Cyclooxygenases-2. *Tropaeolum majus*, *Castilleja tenuiflora* and *Kigelia africana* act downregulating Cyclooxygenases-2 expression. *Origanum vulgare* possesses pleiotropic effects, as it is able to reduce NO and ROS species. Adapted from Leyva-López et al., 2016 and Torres-Rodríguez et al., 2016



**Figure 2:** Species with anti-inflammatory effect mainly based on the regulation of the NF- $\kappa$ B pathway



processed products obtained according to the dialectical rule in TCM (parched with alcohol) and based on local Chinese prescriptions (stir-fried, parched with sesame oil or soil) [30]. The metabolite-based profile obtained on male Wistar rats differs for each treatment with regard to inhibiting the secretion of inflammatory mediators, readjusting the level of potential biomarkers and regulating multiple perturbed pathways. The treatment effects of the drug parched with alcohol and stir-fried are superior to those of other processed products of *A. sinensis* root.

#### B. South America

The genus *Polygala* has been used for a long time to treat several diseases, and especially for pain and inflammation [31]. Aqueous preparations and decoctions of the roots of *Polygala tenuifolia* (“Yuanzhi” in Chinese or “Onji” in Japanese) have been demonstrated to affect TNF- $\alpha$ , IL-1 $\alpha$ , and IL-1 $\beta$  [32,33]. Modern pharmacological studies on another species from the genus *Polygala*, *Polygala molluginifolia* - which is native to Rio Grande do Sul (southern Brazil) and popularly known as “canfora,” one of the ingredients of the local Brazilian tea - showed that a crude hydroalcoholic extract from dried whole plant material, extracted three times for 7 days each, achieved significant anti-inflammatory efficacy in an *in vivo* inflammation model by inhibiting leukocyte migration, exudate concentrations, the activities of some pro-inflammatory enzymes and the production of important mediators in the carrageenan-induced pleurisy murine model [34]. This effect can be attributed, at least in part, to the large amounts of its two main compounds, rutin and 5,3',4'-trihydroxy-6'',6''-dimethylpyrano [2'',3'':7,6] isoflavone, which affect the NF- $\kappa$ B pathway by inhibiting p65 phosphorylation and its translocation into the nucleus, similar to the effect observed with dexamethasone. The potential for the extract to inhibit mechanical and thermal hyperalgesia (heat and cold) in postoperative pain in mice without causing sedation or locomotor dysfunction has been evidenced recently [35]. However, the precise mechanism is not completely known. These authors suggest that this may be mediated, at least in part, by the activation of endogenous opioid receptors and/or by the inhibition of TRPV1 and TRPA1 channels, peripherally, and centrally.

#### C. Southern Africa

The famous species *Harpagophytum procumbens* (“Devil’s claw,” Pedaliaceae), which grows in southern Africa, can still surprise scientists. Although the preparations of the secondary roots of this perennial herbaceous plant are used in every part of the world successfully to treat pain and osteoarthritis and to decrease the need for non-steroidal anti-inflammatory drugs [36,37], the molecular mechanism by which the principal active compound, harpagoside, inhibits the synthesis of inflammatory proteins remains partially unknown. Huang *et al.* [25] investigated the effect of harpagoside on the activity of the nuclear transcription of the NF- $\kappa$ B system. In previous studies of rat mesangial cells, harpagoside failed to attenuate NF- $\kappa$ B translocation to the nucleus, while the whole extracts of *Harpagophytum* succeed. However, Huang *et al.* demonstrated that harpagoside (200  $\mu$ M) inhibited the translocation of NF- $\kappa$ B

into the nuclear fraction in HepG2 cells. This discrepancy suggests that the ability of harpagoside to attenuate NF- $\kappa$ B activity is specific to the cell and/or stimulus and that there are other active components in the extract involved in the inhibition of the NF- $\kappa$ B translocation to the nucleus. The real effect could be defined as modulatory. The structural features required for active principles acting against the NF- $\kappa$ B target have yet to be elucidated. The harpagoside inhibition of COX-2 *in vitro* [38] and the suppression of c-FOS, one of the main components of AP-1 transcription factors, in osteoarthritis chondrocytes [39] have also been reported.

#### D. Europe

*Calea urticifolia* (“Juanislama” in Colombia) is a medicinal plant introduced in Europe from South America in the mid-fifteenth century. It is commonly known in Spain as “Jal de Castilla” and “Hierba del negro.” This species grows in semi-warm and warm climates and is located predominantly in oak forests. It is a shrub, 1-3 m high, with yellow flowers that belong to the Asteraceae (Compositae) family. Local people from Castilla (Spain) use the tea prepared with its leaves as a remedy for gastric ulcers, diabetes and inflammation [40] and as a topical bactericide [41]. The main active compounds from leaves are germacranolide, sesquiterpene lactones with marked cytotoxicity *in vitro* against human tumor cell lines HL60 and SW480 [42]. *C. urticifolia* extract prepared in boiling water (10 g/100 mL) and freeze-dried (yield 14.8%) was able to modulate anti-inflammatory activity through the suppression of the NF- $\kappa$ B signaling pathway by suppressing the nuclear translocation of p50 and p65 subunits of NF- $\kappa$ B that resulted in reduced iNOS expression, inhibited NO/ROS production and the decreased production of pro-inflammatory markers of chronic low-grade inflammation [43]. Phenolic compounds such as caffeoylquinic acids and flavonoids glycosides could be responsible for the anti-inflammatory and antioxidant properties of *C. urticifolia* tea since germacrolides did not inactivate NF- $\kappa$ B as expected and shown in parthenolide [42]. Their pivotal role seems to be involved on Nrf2/ARE pathway activation and the induction of phase II detoxification/antioxidant enzymes [44].

#### E. Australia

In traditional medicine, *Salvia plebeia* (“Sage weed,” Labiatae) is used in the treatment of hepatitis [45] and a variety of inflammatory diseases, colds, and tumors [46]. It is an annual or biennial hairy herb that grows in mountainous regions of many countries such as Australia, Korea, China, India, and Iran. Phytochemical studies on *S. plebeia* have demonstrated that it contains eudesmane-type sesquiterpenoid lactones [47], hispidulin, royleanonic acid, nepetin, eupatorin [46], lignans, diterpenoids, homoplantagin, luteolin, luteolin-7-glucoside, aliphatic compounds, and caffeic acid [45]. Its active compounds include rosmarinic acid and flavones [48]. The dried extract (yield 16.8%) prepared from a previous aqueous extract (dried and ground whole parts of *S. plebeia* in 70% ethanol extract, 1 week) has demonstrated significant anti-nociceptive activity and *in vitro* and *in vivo* anti-inflammatory activity in a dose-dependent manner [46].

An oral dose of 200 mg/kg in male ICR mice showed an inhibition of 66.4% in the writhing number compared to the control group (indomethacin 10 mg/kg). When the extract was prepared in 95% ethanol (10 kg of air-dried and well pulverized aerial parts at 70°C, 5 h and yield 12.35%) and administered orally to 8-week-old male BALB/c mice at a dose of 2 mg/kg, the expression of inflammatory cytokines and chemokines - IL-4, IL-17, MMP-1, and MMP-3 - were inhibited after 54 days [45]. The mechanism of action is partially related to the suppressed I $\kappa$ B $\alpha$  degradation and the nuclear translocation of NF- $\kappa$ B. Nrf2/HO-1 signaling cannot be ruled out as a mechanism underlying the biological effects of *S. plebeia* and its active ingredients [49]. The extract has also demonstrated the inhibition of the Akt and MAPKs pathways, thereby reducing Akt and ERK p38 expression [45].

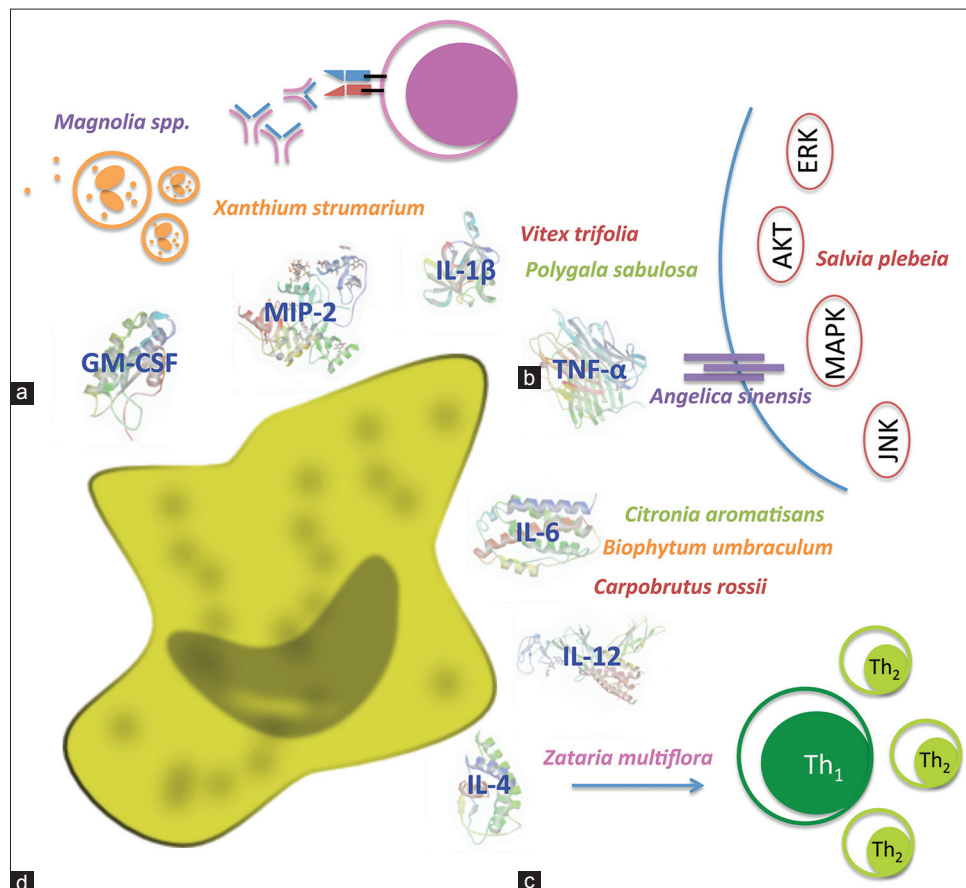
### Anti-inflammatory Role on the Activation of MPHs and other Mononuclear Cells [Figures 3 and 4]

MPHs play an important role in acute and chronic inflammatory response, both locally and systemically [4], and they serve as an

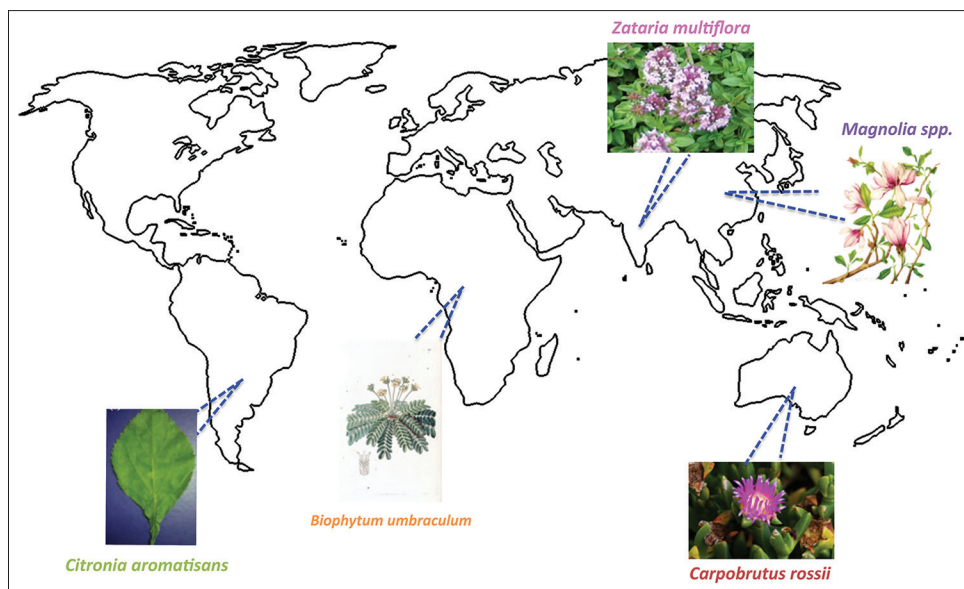
essential interface between innate and adaptive immunity [20]. The activation of MPHs by various stimuli such as bacterial endotoxins, LPS, and viruses massively increases the production of numerous inflammatory mediators, including NO, PGE<sub>2</sub>, and various cytokines such as TNF- $\alpha$ , TNF- $\beta$ , IFN- $\gamma$ , IL-4, IL-6, IL-10, IL-12, interleukin-1 $\beta$  (IL-1 $\beta$ ), granulocyte/MPH colony stimulating factor, MIP-2, monocyte chemotactic protein 1 (MCP-1), and other inflammatory mediators (e.g., 5-HT and L-tryptophan). An increment of some of these mediators (e.g., IL-4) consequently stimulates the activity of B-cells toward the production of IgE, which can exacerbate allergic reactions and stimulate pro-inflammatory responses that are mediated by others mononuclear cells (mast cells, basophils and/or eosinophils). This is particularly the case in allergic diseases such as airway inflammation associated with asthma [50]. These cells also contribute to tissue remodeling, wound healing, phagocytosis and the clearing of apoptotic and necrotic cells [51].

#### A. China

IL-4 is not the only allergic and inflammatory mediator related to asthma. Histamine, PGE<sub>2</sub>, NO, IL-1 $\alpha$ , TNF- $\alpha$ ,



**Figure 3:** Activity on macrophages and other mononuclear cells. a) *Magnolia spp.* inhibit histamine release in mast cells, and *Xanthium strumarium* has the ability to downregulate IgE levels. b) *Polygala sabulosa* and *Vitex trifolia* reduce pro-inflammatory IL-1 $\beta$ , *Citronia aromatisans*, *Biophytum umbraculum* IL-6 and *Carpobrotus rossii* TNF- $\alpha$ , among others. *Salvia plebeia* inhibits Akt and MAPKs pathways, whereas *Angelica sinensis* does so in the TNF- $\alpha$ -activated NF- $\kappa$ B signaling pathway. c) *Zataria multiflora* inhibits total IL-4 and enhances IFN- $\gamma$  gene expression and IFN- $\gamma$ /IL-4 ratio favoring Th<sub>1</sub> activities and suppressing Th<sub>2</sub> functions. C) *Salvia plebeia* inhibits Akt and MAPKs pathways, whereas *Angelica sinensis* does so in the TNF- $\alpha$ -activated NF- $\kappa$ B signaling pathway. D) *Zataria multiflora* inhibits total IL-4 and enhances IFN- $\gamma$  gene expression and IFN- $\gamma$ /IL-4 ratio favoring Th<sub>1</sub> activities and suppressing Th<sub>2</sub> functions.



**Figure 4:** Species with anti-inflammatory effect mainly based on acting upon macrophages and other mononuclear cells

and platelet active factor (PAF) but also play an important role. *Flos magnoliae* (Chinese name “Xin-Yi” or “Shin-I”) is one of the most commonly used Chinese medicinal herbs with a long history of clinical application for managing the symptoms of allergic rhinitis and sinusitis [52]. In patients with mild to moderate asthma, a purified extract improved both the asthma-related symptoms and the pulmonary function after 8 weeks [53]. The drug consists in the dried flower buds of *Magnolia* spp. The Pharmacopoeia of the People’s Republic of China [28] includes three magnolia species: *Magnolia biondii*, *Magnolia Denudate*, and *Magnolia sprengeri*. Among these, *M. biondii* is the most commonly used form of *F. magnoliae*, which accounted for more than 80% of the market in 2003 [54]. A dry extract of the first two species (from a previous absolute ethanol extract, 1 g fine powder of dried flower buds in 60 mL ethanol, three static cycles at 100°C) 05 mg/mL of absolute ethanol or above in a concentration- and inhibition-dependent manner [55]. Lignans from *F. magnoliae*, including magnolin, magnoshinin, magnosalin [56], lirioretinol-b-dimethyl ether, pinoretinol dimethyl ether, fargesin, demethoxyaschantin, and aschantin may contribute to the pharmacological activities of *M. biondii*. These bioactive lignans have been shown to inhibit various inflammatory mediators such as the PAF, cytosolic phospholipase A2 (PLA), hexosaminidase, lipoxygenase (LO), the complement system and the production of leukotriene (LT) C<sub>4</sub> [53]. Although magnolin, adopted by the Chinese pharmacopoeia as a quality control marker, and fargesin have been linked to beneficial therapeutic effects, the assay demonstrated that there were no correlations between the contents of magnolin and fargesin and the inhibition of *F. magnoliae* on induced histamine release.

#### B. South America

The ointment prepared by placing crushed leaves of *Critonia aromatisans* (synonym of *Eupatorium hemipteropodum*, Compositae, in Spain commonly called “Trebol Oloroso”)

in a fire along with melted petrolatum is used for anti-inflammatory and anti-arthritis remedies. It can be applied directly to the painful area as a semi-solid preparation. It allows the lipophilic compounds that are responsible for the pharmacological activity and captured by the petrolatum to be absorbed. Leaves in decoction can also be used as a poultice. Despite this, the Compositae family is one of the most frequent causes of allergic plant contact dermatitis and bullous allergic contact dermatitis [57]. Strong anti-inflammatory activity has been demonstrated in preclinical *in vivo* assays conducted in BALB/c mice and in NIH mice only for the n-hexane extract [4]. Their results suggest that part of the mechanism of action of the n-hexane extract of *C. aromatisans* is due to its inhibitory effect on MPHs. Some of the classical pro-inflammatory mediators produced by MPHs, including TNF- $\alpha$ , IL-1 $\beta$ , IL-6, and NO, and their release is reduced significantly in cell culture from a concentration of 50  $\mu$ g/mL. The compounds involved and the mechanism of action are not clear. The probable presence of the species of cyclocolorenone, a compound with an  $\alpha$ ,  $\beta$  unsaturated cyclopentenone ring (a reactive structural element similar to sesquiterpene lactones), and stigmaterol, a phytosterol that inhibits some pro-inflammatory and pro-degradative mediators involved in inflammation, may contribute to or produce the anti-inflammatory effect observed.

#### C. Africa

The annual herb *Biophytum umbraculum* (Oxalidaceae), which is commonly found in tropical and subtropical Africa and Asia, is a highly valued medicinal plant used to treat hemorrhoids, wounds, stomach aches, fevers [58], dysregulated inflammation, conjunctivitis, vaginitis and colon illnesses, among others [59]. In Mali, the aerial parts are used to treat both children and adults, and no toxicity has been reported. The most common way to prepare and administer the medicine is to mix the powder of the flowering aerial parts with water; it can be

applied topically, massaging to facilitate the transdermal bioavailability of the compounds, or it can be taken orally [59]. Cassiaoccidentalin A, isovitexin, and isoorientin are flavone-C-glycosides that are isolated from the EtOAc-soluble fraction of the methanol crude extract [58]. They revealed strong antioxidant activity but were inactive when the inhibition of LPS-induced MPHs was tested, and this was in spite of the high dose-dependent inhibition showed by the EtOAc extract. The activity appears to be due to unidentified compounds [59].

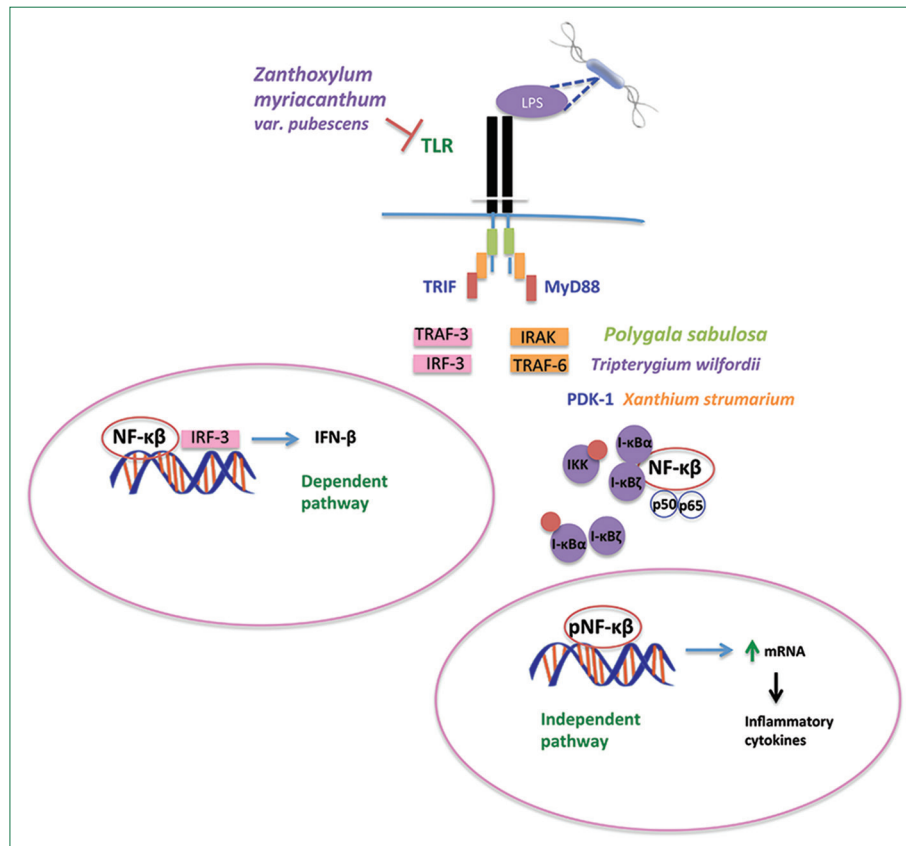
#### D. India

The inflammatory condition, particularly in allergic diseases such as airway inflammation associated with asthma, is regulated by the balance of Th<sub>1</sub>/Th<sub>2</sub> cells. An inappropriate response or change in Th<sub>1</sub>/Th<sub>2</sub> balance, as well as an uncontrolled activation of Th<sub>2</sub>, can cause hyper-reactivity, resulting in asthma disease. *Zataria multiflora* (or *Zataria bracteata*), also called “Avishan-e-Shirazi” or “Shirazi thyme,” is a perennial plant belonging to the Lamiaceae family. It is commonly prescribed in Iranian traditional medicine for its antiseptic [60], analgesic, carminative, anthelmintic, and antidiarrheal properties [61]. An aqueous-ethanolic extract (ethanol 50%/water 50:50) was administered to guinea pigs sensitized to ovalbumin. It inhibited the total IL-4 and enhanced IFN- $\gamma$  gene expression and the IFN- $\gamma$ /IL-4 ratio, which is an index for Th<sub>1</sub>/Th<sub>2</sub> balance, at doses of

30 mg of extract per day [62]. It, therefore, potentiated Th<sub>1</sub> activities and suppressed Th<sub>2</sub> functions. Sensitized animals treated with the extract showed significant improvement in all histological changes of the lung including interstitial inflammation, interstitial expansion, atelectasis, and epithelial damage. There were no adverse effects on treated animals. The anti-inflammatory effect of *Z. multiflora* has been associated, at least in part, with its flavonoids and essential oils, but other active substances of the plant might also be involved [61,63]. Further investigations are needed to unravel the anti-inflammatory properties of this plant, which is employed not only for its thymol and carvacrol content (higher than 65% in both fresh and dried plant), but also for its potential to treat coughs, bronchitis, pneumonia and laryngitis, among others, when multidrug-resistant strains are involved [64].

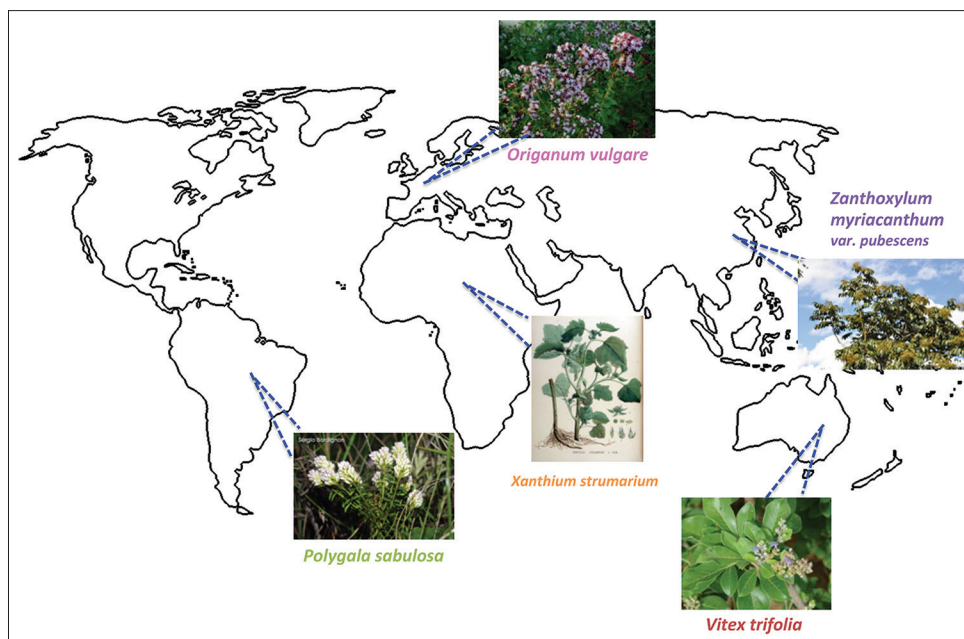
#### E. Australia

*Carpobrotus rossii* (commonly “pigface”), a haplophyte from the Aizoaceae family, is a salt-tolerant coastal succulent ground cover that is native to southern regions of Australia, including the island state of Tasmania. There are many anecdotal (verbal) accounts of *C. rossii* juice being used by local Aboriginals and early European settlers as a traditional remedy for a number of ailments, including upper respiratory tract and throat infections, gastrointestinal upset and itching caused by spider and tick bites, and as an astringent used



**Figure 5:** Toll-like receptor-mediated actions. *Zanthoxylum myriacanthum var. pubescens* demonstrates suppresses the expression of TLR4 in LPS-activated cells. *Polygala sabulosa* inhibits the activation of TLR4 by LPS. *Tripterygium wilfordii* affects the expression of TRAF-6, which is downstream to the MyD88 signaling pathway, and *Xanthium strumarium* blocks PDK1 and Akt kinase activity, inhibiting the formation of the PDK1/Akt complex. Adapted from Liao *et al.*, 2013 and Hossen *et al.*, 2016





**Figure 6:** Species with anti-inflammatory effect mainly based on a toll-like receptor-mediated action

externally on wounds, burns, eczema and bluebottle and jellyfish stings [65,66]. Geraghty *et al.* (2011) demonstrated that pretreatment with a dry extract (100  $\mu\text{g}/\text{mL}$  of RPMI 1640 media formulation) of fresh juice from succulent leaves reduced IL-10, TNF- $\alpha$  and MCP-1 in peripheral blood mononuclear cells by 57, 72 and 81%, respectively, when stimulated with 5  $\mu\text{g}/\text{mL}$  of LPS. It also reduced MCP-1 by 74%, at a dose of 100  $\mu\text{g}/\text{mL}$  of RPMI 1640 media, when 5  $\mu\text{g}/\text{mL}$  of phytohaemagglutinin A (PHA) was added. The *C. rossii* extract was a more effective inhibitor of cytokine release in the presence of LPS than PHA, indicating the inhibition of cytokine release from a wide variety of leukocytes, including B-lymphocytes, monocytes, and MPHs. No *in vivo* studies were carried out. Fractionation of the extract revealed an important polyphenolic fraction consisting of flavonoids (epicatechin, among others) and tannins, which is consistent with previous assays where epicatechin at concentrations around 200  $\mu\text{g}/\text{mL}$  suppressed both RNA expression and the secretion of TNF- $\alpha$  and MCP-1 by NR8383 MPHs [67].

### Toll-like Receptors Mediated Actions [Figures 5 and 6]

Toll-like receptors, a subtype of the pattern recognition receptors, are able to identify structural components present on the surface of pathogens (e.g., lipids, carbohydrates, peptides and nucleic acids) that are unique to bacteria, fungi and viruses. These structural components, which are called pathogen-associated molecular patterns, are present on the surface of immune-competent cells such as monocytes/MPHs, dendritic cells, neutrophils and endothelial cells, and signal to activate a host's inflammatory response [68]. TLR4 has been regarded as the main sensor for the recognition of Gram-negative bacteria and as critical upstream mediators that trigger excessive inflammatory cascades [69].

#### A. China

Recently, the essential oil from the fruits of *Zanthoxylum myriacanthum* var. *Pubescens* (or “Maqian”) have been demonstrated to possess healing activity against dextran sulfate sodium- induced intestinal inflammation in mice [70]. *Z. myriacanthum* is a TCM herb native to the Xishuangbanna Dai Autonomous Prefecture, Yunnan Province, China, distinguished by its soft hairy rachis, leaves, and petioles. The fruits are commonly consumed as a spice and used for the treatment of gastrointestinal disorders (e.g., abnormal pain), parasite invasion and centipede bites [71]. When they were extracted using the hydrodistillation method and the resulting essential oil was administered to TPH-1 cells (v/v 0.01%, 0.02%, 0.04%, and 0.05%), the expression of TLR4 in LPS-stimulated THP-1 cells was effectively suppressed in a dose-independent manner. The essential oil effectively prevented the LPS-stimulated increase in TLR4 expression and markedly blocked the downstream IKK and I- $\kappa$ B phosphorylation. Moreover, the pro-inflammatory cytokines, including TNF- $\alpha$  and IL-1  $\beta$ , were also suppressed.

#### B. South America

*Polygala sabulosa*, popularly known as “Timutu-pinheirinho” in Brazil, is a small herb with an abundant number of secondary metabolites, including coumarins, saponins, lignans, flavonoids, steroids, and many xanthenes [72]. They are used in folk medicine for the treatment of disorders of the bowel and kidney, as a tonic remedy and as a topical anesthetic and expectorant. In male Swiss mice, the peritonitis model was induced by LPS injection, and the pretreatment with hydroalcoholic extract (500 g air-dried whole plant ground to a powder and extracted at room temperature with 96% ethanol for 14 days) in doses from 3 mg/kg demonstrated an ability to reduce pro-inflammatory (IL-1  $\beta$ , TNF- $\alpha$ , and IL-6) and increase

anti-inflammatory (IL-10) cytokines levels in the peritoneal leakage [3]. These authors suggest that the extract may be acting directly or indirectly to inhibit the activation of TLR4 by LPS. As is well-known, LPS, a component of the outer membrane of gram-negative bacteria, is a potent activator of MPHs and an exogenous ligand of TLR2, which is expressed in lymphoid tissues, T cells, and MPHs, and TLR4, which is expressed in monocytes, MPHs, dendritic cells and Th1 and Th2 cells. LPS may regulate TLR-2 expression directly and/or through TLR4 [73]. TLR4 signaling involves two pathways: One is dependent on the activation of myeloid differentiation primary response gene 88 (MyD88), and the other is MyD88-independent and unique to TLR3 and 4 [69]. Notably, the MyD88-dependent pathway leads to the transcription of pro-inflammatory genes, resulting in increases in the production of pro-inflammatory cytokines [68,74,75]. Through MyD88-dependent pathways, the IKK complex is activated and induces the expression of inflammatory cytokines through the nuclear translocation of NF- $\kappa$ B. The MyD88-independent pathway utilizes the adapter TRIF to mediate the activation of IRF-3 and the production of type-1 interferons. The suppression of NF- $\kappa$ B activation, direct or indirectly by *P. sabulosa* extract - for example, through the MyD88-dependent pathway - cannot be ruled out.

#### C. South Africa

Among the plants in the genus *Xanthium* (Asteraceae), *Xanthium strumarium*, commonly referred to as “cocklebur,” has traditionally been used as an herbal medicine in South Africa [76]. When mature, this robust, annual weed bears numerous oval, brownish, and spiny burs. The entire plant has been used as a medicine to cure inflammatory ailments such as rheumatism and to relieve constipation, diarrhea and vomiting, chronic bronchitis and rhinitis [23,77]. The essential oil is highly appreciated [78]. Its bioactive compounds include glycosides, phytosterols, phenolic acids, and xanthiazones. Only the seeds in the burs and young seedlings (cotyledonary leaves) contain the toxic principle, carboxyatractyloside [76]. The methanolic extract from the whole plant demonstrated the suppression of LPS-induced phosphorylation of AKT and IKK $\alpha/\beta$  through TLR2 and 4 by blocking PDK1. It also suppressed the Akt kinase activity and inhibited the formation of the PDK1/Akt complex in cells treated with RAW 264.7 [22]. It leads to the reduced production of IL-6 without affecting IL-1 $\beta$  or TNF- $\alpha$  [23]. The main component that may be involved in PDK1 regulation is resveratrol [22]. The extract has no effect on COX-2 expression at either the mRNA or protein level [23]. NO and PGE<sub>2</sub> levels were also diminished. Upregulation of 15-hydroxyprostaglandin dehydrogenase (15-PGDH), which produces biologically inactive 15-ketoprostaglandins from active PGE<sub>2</sub>, has been hypothesized as a possible explanation. The reduced production of IL-6 has been confirmed by Wang *et al.* (2015) for caffeoylxanthiazonoside isolated from *Z. strumarium* fruits and administered by intraperitoneal injection on a sepsis mice model at doses of 10 mg/kg or higher, but in this case, it was TNF- $\alpha$  production that decreased. The same compounds demonstrated favorable anti-allergic effects and the ability to ameliorate

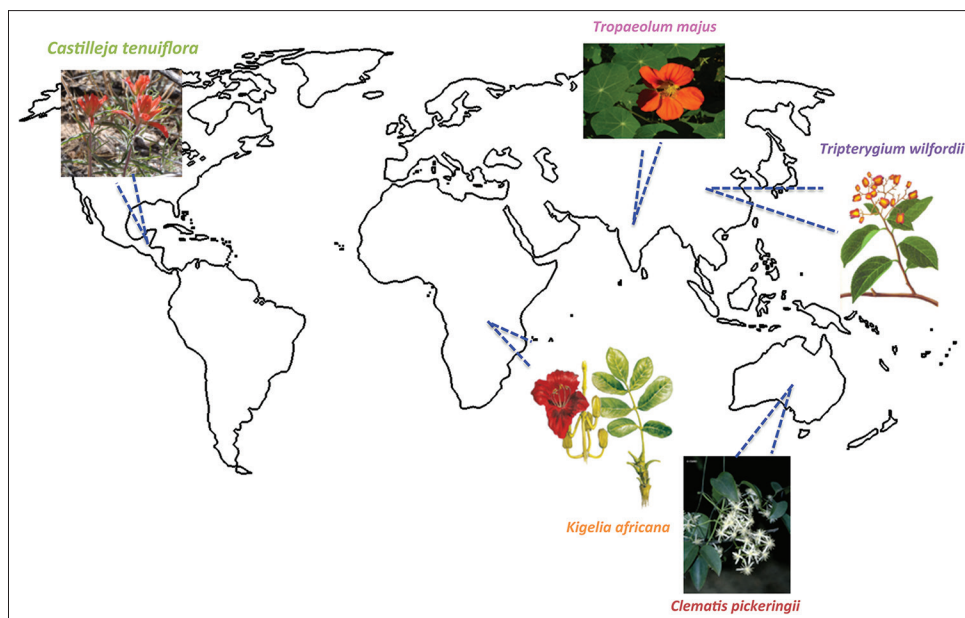
the nasal symptoms and to downregulate IgE levels in an allergic rhinitis rat model [79].

#### D. Europe

Oregano is the common name for a herb primarily derived from a wide group of plant genera and species used throughout the world in cooking. At least, 61 species from 17 genera belonging to six families are given the name oregano, though the Verbenaceae and Lamiaceae families are the most important [12]. In Europe, *Origanum vulgare* L. is the species most often commercialized as oregano. It is a widespread species native throughout the Mediterranean region, in most parts of the Euro-Siberian region and the Irano-Turanian region [80]. *O. vulgare* has been collected since ancient times to flavor traditional dishes and to relieve various complaints such as convulsive coughs, colds, skin diseases, digestive disorders, headaches, and inflammation-related disorders [81]. The leaves and flowering branches are used in fresh infusions and decoctions and as hydroalcoholic extracts. The bioactivity of the active compounds depends on the preparations consumed [82]. The phenolic acids, flavonoids, and monoterpenes deriving from the “cymyl”-pathway (mainly carvacrol and/or thymol and their biosynthetic precursors *c*-terpinene and *p*-cymene) present in the essential oil are hypothesized to possess anti-inflammatory properties [80]. When the essential oils of lavender, salvia, and oregano were diluted in unscented cream at 3% concentration (in a 2:1:1 ratio) and used daily to massage the lower abdomen of primary dysmenorrhea patients, the blended essential oils demonstrated analgesic properties [83]. With the growing number of reports on the biological activity and nutritional benefits derived from oregano consumption, the identification of the compounds responsible for its activity and the study of its anti-inflammatory potential are relevant and important [12,84]. Both polyphenols, monoterpenes, and sesquiterpenes are active compounds of oregano for which an anti-inflammatory mechanism model based on the amelioration of pro-inflammatory mediators (NO and ROS) and mitochondrial and COX activity produced by LPS-activated MPHs through TLR4 has been proposed [12].

#### E. Australia

*Vitex trifolia* L. (simpleleave chastetree, Labiatae) is a tropical shrub or tree (up to 5 m tall) that grows mainly in the coastal areas and is widely employed by Pacific islanders to cure numerous illnesses [85]. The leaves are used in maceration or decoction, both internally and externally, as a remedy to cure illnesses and especially to abrogate diseases that may involve inflammatory processes [18]. For example, it can be heated and rubbed on the forehead to treat headaches, and it can be applied topically as an infusion to relieve fever or alleviate pain derived from rheumatism and sprained joints [85,86]. The traditional aqueous decoction of *V. trifolia* leaves (after lyophilization, 1 mg/mL) has shown the ability to decrease the expression of numerous inflammatory mediators (e.g. cytokines, chemokines, COX-2) through the diminution of the nuclear translocation of the transcription factor NF- $\kappa$ B, which is related to the inhibition of the expression of the NF- $\kappa$ B p50 subunit (but interestingly, not the p65 subunit) after TLR4 activation [18]. It also inhibits IL-1  $\beta$  and



**Figure 7:** Species with anti-inflammatory effect mainly based on cyclooxygenases and LOXs inhibition

caspace-3 in RAW 264.7 cells, since it is able to downregulate apoptosis due to non-activation of caspase 8, which allows it to avoid the apoptosis of cells. A flavonoid, vitexicarpin (also named casticin), has been reported as the molecule responsible for significant anti-inflammatory effects on acute inflammation and on cell proliferation [86,87]. Among others, it was shown to exert immune-modulatory effects by inhibiting monocyte oxidative burst, chemotactic action on stimulated neutrophils, T- and B-lymphocyte proliferation, the inflammatory activity of isolated human neutrophils and interference with the activity of the STAT1. It also played a vascular protective role through the suppression of NF- $\kappa$ B nuclear translocation.

### Inhibition of COX and LO [Figure 7]

When the efficacy of plant extracts on inflammatory conditions needs to be investigated and/or compared [6], researchers fully study the inhibitory effect on the biosynthesis of important inflammatory mediators and PG, for example, PGE<sub>2</sub> and PGD<sub>2</sub>, which are potent dilators of vascular smooth muscle that account for the characteristic vasodilatation and erythema (redness) in acute inflammation and symptoms such as fever and pain—from free cell membrane arachidonic acid (AA) liberated by PLA<sub>2</sub> and catalyzed by the molecular targets COX-1, COX-2, 5-LO, and 12-LO. It was initially suggested that the isozyme COX-1 was constitutively expressed in most tissues and involved in the regulation of physiological “housekeeping” (e.g., in the stomach, COX-1 is important for mucosal fusion, bicarbonate production, and mucus production [5]) and that COX-2 was an isoform that could be induced in pathological conditions by inflammatory stimulation. Selective COX-2 inhibitors were developed to prevent gastrointestinal side effects caused by the inhibition of COX-1 [88]. However, recent studies have demonstrated that COX-1 and COX-2 have overlapping actions and that are both involved in homeostasis

processes. COX-1 has a significant role in the synthesis of pro-inflammatory PGs and may be induced at the site of inflammation, and COX-2 is constitutively expressed in some tissues, including the brain and kidneys [89]. Furthermore, inhibiting the COX pathway shunts the metabolism of AA toward the 5-LOX pathway [90]. The 5-LOX pathway generates an important class of inflammatory mediators, including LTs, which play a major role in asthma and vascular changes during the inflammatory process. Therefore, in recent years, dual inhibitors of both the COX and LOX pathways are seen as a promising new approach to inhibiting inflammation with no or low toxicity, and they could be an important treatment for many inflammatory disease states [88,91].

#### A. China

Of 46 Chinese materia medica vine plants, 44 have been used to treat rheumatism and related inflammatory diseases [92], alleviate pain in joints and muscles, relieve fever and stiffness in the limbs and expel “wind-dampness” [93], a term related to rheumatic fever, rheumatoid arthritis, and osteoarthropathy [91]. Of these plants, *Tripterygium wilfordii* (“lèi gong téng” in China, *Celastraceae*) roots and stems and *Trachelospermum jasminoides* (“confederate-jasmine”, *Apocynaceae*) stems have been used in decoctions for centuries. COX-1, COX-2, and 5-LOX inhibition assays were carried out to evaluate the anti-inflammatory effects of these traditionally used vine plants. The dry extracts (from previous one in absolute ethanol under 6° for 8 h, reconstituted in ethanol before each experiment) of both *T. wilfordii* roots and stems (DER 1.08:30) and *T. jasminoides* stems (DER 0,85:30) demonstrated significant inhibition of COX-1 (inhibitory concentration (IC<sub>50</sub>) 27 ± 1  $\mu$ g/mL and 35 ± 2  $\mu$ g/mL, respectively) and COX-2 (IC<sub>50</sub> 125 ± 8  $\mu$ g/mL and 138 ± 7  $\mu$ g/mL, respectively). Only *T. wilfordii* extract showed linear regression (IC<sub>50</sub> 22 ± 2  $\mu$ g/mL) for 5-LOX [91]. Although *T. wilfordii* extract showed a significantly higher

IC<sub>50</sub> value on COX-2 than indomethacin under the same experimental conditions ( $P < 0.01$ ), there is ample evidence that *T. wilfordii* is toxic and that its use has resulted in cases of leukopenia and thrombocytopenia. Therefore, complete cytotoxicity studies should be undertaken and reported before further clinical practice [94]. Qin *et al.* [95] reported the potential therapeutic effect of *T. wilfordii* on inflammation through the inhibition of the expression of TLR4 affecting the expression of TRAF-6, which is downstream of the MyD88 signaling pathway, thereby suppressing the activation of NF- $\kappa$ B and reducing the release of inflammatory factors such as TNF- $\alpha$  and IL-1 $\beta$ .

#### B. South America

*Castilleja tenuiflora* (also known as *C. angustifolia* and *C. canescens*, popularly “cola borrego” in Spain) is an annual small perennial shrub belonging to the *Orobanchaceae* family that is distributed in disturbed areas of pine-oak temperate forests of the Southern United States and Mexico [96]. In The History of the Plants of New Spain (16<sup>th</sup> Century), this species was recorded under the Náhuatl name “Atzoyatl.” It is described as having a “hot nature” and root preparations that heal colics caused by fecal mass retention [97]. It is commonly known in Mexico as “garaiiona,” “cola de borrego” (lamb tail) or “hierba del cancer” and in English as “Indian paintbrush” [98]. It is harvested wild for traditional use. The decoction of its leaves has been used in Mexican traditional medicine to treat coughs, dysentery, nerves, nausea, and vomiting as well as hepatic and gastrointestinal diseases [96]. *C. tenuiflora* accumulates iridoid glycosides, such as aucubin and geniposidic acid, in its aerial parts and roots. These glycosides have *in vitro* antitumor and cytotoxic effects [99] as well as neuroprotective, immunomodulatory, hepatoprotective, cardioprotective, and anti-inflammatory (COX-2 and COX-1 related) effects [100]. In addition to iridoid glycosides, the phenylethanoid glycosides verbascoside and isoverbascoside have been detected in the genus *Castilleja* and isolated from the roots and aerial parts [96,98]. PhGs are natural compounds that can be absorbed by human intestinal cells, and they are potent anti-inflammatory agents because they inhibit the accumulation of pro-inflammatory molecules such as NO and cytokines along with the expression of the COX-1 and COX-2 [101]. The presence of these compounds in *C. tenuiflora* could be related to the significant effect of 20% (20.01  $\pm$  3.45%) inflammation inhibition produced by 1 mg/ear of a dry extract from a previous methanolic one obtained from the aerial parts of *C. tenuiflora* (255 g of whole plants extracted twice with 0.4 L absolute ethanol) in a topical model of inflammation [TPA-induced ear edema in male ICR mice (1 mg/ear and n=5)] [96]. In contrast, the control, indomethacin, showed 40% inhibition.

#### C. Africa

Among the African medicinal plants, *Kigelia africana* (also *K. pinnata* or “sausage tree”) of the family Bignoniaceae happens to be one of the most recognized [102]. Locally known as the cucumber or sausage tree because of its huge fruits (which average 0.6 m in length and 4 kg in weight), it can grow to more than 20 m tall [103]. People in different parts of the world have claimed that parts of this plant serve various purposes, but there is not enough scientific

research to back up their claims. In Ivory coast, eating the bark powder daily and bathing in its maceration are folk and traditional treatments for articular rheumatism [104]. In Sudan, Senegal, Tanzania, Benin, and Kenya, the decoction of the stem bark mixed with soda or cow milk for oral use or flour for dressing inflamed body parts is used for waist pain, wounds [105], ulcers or sores. For toothaches, the powdered bark is applied around the inflamed teeth [106]. The mature fruits and roots are also used to treat abdominal pain and fever. Researchers have evaluated the anti-inflammatory activity of several parts of the plant, including the stem bark and roots. The ethanolic stem bark extract (500 g powdered bark with 2.5 L of absolute ethanol, 72 h, yield 3.78% w/w) has been researched for its activity against carrageenan-induced inflammation on the hind paws of rats (a classic and highly reproducible method for assessing the acute inflammatory responses in antigenic challenges and irritants) and for its analgesic properties in the hot plate test and mouse-writhing assays [103]. The dry extract in doses of 200 mg/kg produced a higher inhibition of the synthesis and release of PG than aspirin (100 mg/kg), which resulted in a dose-dependent anti-inflammatory effect. This is most likely the mechanism by which the analgesic effect occurs.

#### D. India

Nasturtium (“Indian cress,” *Tropaeolum majus*), an herbal plant from the order *Brassicales*, is traditionally employed in the treatment of cardiovascular disorders for its antihypertensive and diuretic effects [107]. Its effects on inflammation and microbes meet the 1978 German Commission E standards for herbal medicines [108]. This species contains high amounts of benzyl glucosinolate. Some authors [109,110] attribute its biological effects, at least the anti-bacterial and the anti-inflammatory ones, to the products of its enzyme-mediated hydrolysis. Tran *et al.* (2016) demonstrated that aqueous nasturtium plant extract (1 g of whole plant powder in 10 ml of distilled water [pH 6.32] or DMSO at 37°C for 30 min at 100 rpm) at a concentration of 111  $\mu$ g/mL not only selectively inhibits COX-2 protein expression and PGE<sub>2</sub> release but also has no impact on COX-2 enzyme activity in primary human peripheral mononuclear cells (PBMCs). They found that 5-LOX protein expression was not regulated at any of the tested plant extract concentrations, even though when PBMCs were pretreated with nasturtium extract (333  $\mu$ g/mL) followed by 1  $\mu$ g/mL LPS and 1  $\mu$ g/mL fMLP, the release of the LT B<sub>4</sub> was inhibited (by half) compared with the negative control. The authors suggest that the reduced COX-2 protein levels that follow pretreatment with the compounds could be related to a temporary inhibitory effect on ERK1/2 downstream signaling and blocking of the c-Jun activation involved in forming the early response transcription factor AP-1, which starts the transcription of pro-inflammatory cytokines (e.g., TNF- $\alpha$ ). A 90% ethanolic extract of *T. majus* leaves a lyophilized yield of 14% and showed no sub-chronic toxicity after a 28-day long oral treatment in Wistar rats at a dose of 750 mg/kg [111]. These results suggest that this species is safe. However, other toxicological studies are necessary to evaluate the overall safety of this plant.



### E. Australia

The species *Clematis pickeringii*, *Clematis glycinoides* (“traveler’s joy” and “headache vine”), and *Clematis microphylla* have been traditionally used in Australia to treat inflammatory conditions [6]. Both indigenous Australians and bushmen have used the crushed foliage to cure headaches and colds by inhaling the strong and sharp aroma [112,113] and applying the juice, freshly ground leaves or bark to the painful area [114]. The dry extract of *C. pickeringii* stems (mixed with PVP 5% to remove the tannins that have been reported to produce antiphlogistic activity during the preparation of extracts) from a previously ethanolic plant (absolute ethanol is 500mL x3, 48h each at room temperature with a final yield of 4.3%) showed COX-1 ( $IC_{50} 73.5 \pm 1.2 \mu\text{g/mL}$ ), COX-2 ( $IC_{50} 101.2 \pm 1.2 \mu\text{g/mL}$ ), and 5-LOX ( $IC_{50} 29.3 \pm 2.3 \mu\text{g/mL}$ ) inhibition. *C. pickeringii* stems activated the protein expression of PPAR $\alpha$  and PPAR $\gamma$ , which then cause cell replication, differentiation, and inflammatory responses in HepG2 cells ( $60 \mu\text{g/mL}$ ; [89]). Experiments performed this way showed better results than previously published studies in which the extraction was carried out with absolute ethanol for 12 h at 70°C and produced a 4.7% yield [6]. These authors speculate that *C. pickeringii* contains active ingredients that act as a natural peroxisome proliferator-activated receptor (PPAR $\alpha$ ) and PPAR $\gamma$  ligands.

## AN OVERVIEW

There are many plants used to treat inflammatory diseases worldwide. Here, interesting examples of early approaches to deciphering the enigma of the pharmacological relevance and mechanisms from plants used in different cultures have been provided. As has been shown, “traditional medicine” around the world has directly or indirectly discovered, without accurate scientific knowledge, the same anti-inflammatory actions. Nonetheless, the ethnopharmacological investigation of these species is still relatively limited, and the state of science to date on the selected species is still poor and inconclusive. The cellular and molecular mechanisms underlying the anti-inflammatory actions of these plants or their chemical ingredients remain poorly characterized. Observation, description, and investigation of the ingredients, their effect and these indigenous drugs would allow the development of an “ethnopharmacy” process that encompasses relevant disciplines, such as pharmacognosy, pharmacology, toxicology, and drug delivery, to apply knowledge from orally transmitted medical systems to drug development [115] in an evidence-based and scientifically rational approach.

However, inflammation is a complex combination of processes, some of which are not fully understood, involving several interdependent events that vary in duration, intensity, and consequences over time and between people. Thus, the therapeutic strategy for treating inflammation should be streamlined. If the ailment is different, then why should the remedy be the same? Researchers have paid close attention to this issue in recent decades. Using a model analysis, Kell [116] demonstrated how targeting a particular step in the signaling

pathway of the transcription factor NF- $\kappa$ B can have qualitatively (directionally) different effects depending on the actual state of the system and whether systems are diverse. In the case of phytomedicines, combinations of ingredients are subject to considerable batch-to-batch variability since this will depend on where plants go, harvesting techniques, storage and the preparation of decoctions [16] where the interactions between the components of the medicine and potential molecular targets (required for optimal effect) are more complex than those associated with a single chemical entity in no particular step. This is far from simple. The same approach could be applied to TCM, a complex theoretical system that encourages interactions and synergies between the various phytomedicines comprising any given therapy.

A characterized compound or group of compounds with a perfectly defined mechanism of action at a particular dose fulfills the negative requirements (such as toxicity) inherited from classical pharmacology. The new trends suggest an integrative approach in which a wide variety of compounds act together on multiple targets to produce a final action through a balance resulting from minor changes. The researchers have made suggestions wherever possible about “the most active principal compounds” involved in the events. However, in this way, an assumption is made. The plant has one or a few ingredients that determine its therapeutic effect, what’s called “the silver bullet method” [117]. In this method, the described effects would not be explained completely. In recent years, “the shotgun approach,” which has been understood as a therapeutic strategy that targets multiple parts of an organism, has gained increasing acceptance [118].

Omic technologies and methods and systems biology approaches will become principal tools in current and future endeavors to integrate traditional and modern medical systems. Through them, classical concepts will fit into new strategies of coping with chronic and emerging diseases. An integrated approach using genomics, transcriptomics, proteomics, and metabolomics as well as phytomedicine for the assessment of the mode of action of multidrug treatments will likely yield the most reliable results, but it remains the great challenge for the future [119]. Promising results can be expected in the inflammation field. Ulrich-Merzenich *et al.* (2007) use microarrays to obtain the gene expression profile (mRNA) of willow bark extract STW-33-1, quercetin, diclofenac, and acetylsalicylic acid in human chondrocyte cultures and willow bark extract STW-33-1 in the blood cells of rats. Gene expression rates were up- or down-regulated differently for each substance, which clearly demonstrated that they had specific expression profiles. The modulation of genes is not the only effect a compound/extract could promote. It is converted at the protein level, and the metabolomics is understood quantitatively and completely, which has led to patterns associated or not associated with anti-inflammatory results. Classical pharmacology can add onto this step each compound membrane disturbance, receptor agonism or antagonism and protein inhibition or stabilization, among other things. Even in systems biology, the protein networks, and regulatory feedback loops must be taken into account. If an extract is administered,

the complexity grows greatly. The combination of constituents could yield a new, fully differentiated state and the effect could or could not be (synergism or antagonism) dose-dependent. The interactions could be much more sophisticated.

Despite the high level of complexity and cost of the omic techniques, they are the only way the pharmacological action of many species can be fully understood. They are the key to a rational and fully accepted form of phytotherapy. The application of “omic” technology unfolds the possibility to investigate phytopreparations without prominent active principle(s) for their complex mechanisms of action and helps us to rationalize the therapeutic superiority of many plant extracts over single isolated constituents” [119]. Furthermore, through them, the prescription could be selected according to the patient’s needs in individualized medicine or more generally in stratified medicine targeted at subgroups of patients. In terms of ailment, developing the appropriate drug for each health problem and physiological condition means assessing “personal safety,” shortening the drug development process and prompting cost reduction. How this could be introduced into regulatory laws to comply with the legal conditions is another matter.

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