

Perspectives on 'Kamsaharitaki': an Ayurvedic Formulation for COVID-19 related Multisystem Inflammatory Syndrome (MIS)

Vaibhav Bapat^{1*}, Anup Pande², Sagar Narode³, Surendra Vedpathak⁴

Abstract

Background and Aim: Angiotensin-converting enzyme 2 receptor (ACE2), together with Transmembrane protease serine 2 (TMPRSS2), is a protein receptor for SARS-CoV-2 virus in the host subject; expression of ACE2 and TMPRSS2 reveals the multidimensional character of COVID-19 infection. SARS-CoV-2 Prominently induces pulmonary and systemic injury with other synergistic mechanisms. Preexisting chronic inflammatory conditions markedly sustain and aggravate the severity and cytokine storm. Inflammatory responses are closely linked with COVID-19 severity and complications. Role of Reactive oxygen species (ROS) is crucial and owing the demand of polyherbal combinations with antioxidant potential for their preventive and therapeutic aspects. Ayurveda intended to develop potential immune mechanism in the host while dealing with infectious diseases. 'Kamsaharitaki' a polyherbal formulation predominantly indicated in inflammatory conditions targeting multiple systems is found to be most appropriate to restrain Multisystem inflammatory syndrome (MIS) associated with COVID 19. To support and establish this; phytopharmacological exploration is decisive. **Methodology:** A keen exploration of in vitro, in vivo studies with electronically published data limited to Pubmed search engine interrelated to phytochemicals and pharmacological properties of each solitary herb along with predefined groups of herbs constituting this formulation is carried out. **Results and Conclusion:** This revealed presence of numerous phytochemicals with comparable pharmacological properties. Dashmula (group of 10 herbs of this formulation) illustrated statistically significant anti-inflammatory, antioxidant and anti-platelet ($P < 0.05$) potentials. Terminalia chebula a chief constituent exhibited 3CLpro inhibitory potential and other ingredients possess supportive properties. This will provide a potential evidences for further research.

*Author for Correspondence

Vaibhav Bapat

¹Panchakarma Vaidya, Department of Panchakarma National Institute of Ayurveda, Deemed to be University, Jaipur, Rajasthan, India

²Associate Professor, Department of RSBK, Ayurveda Mahavidyalaya and Hospital, Risod, Dist-Washim, Maharashtra, India

³Associate Professor, Department of Agadtantra and Vyavahar Ayurved, Shri Saptashrungi Ayurveda Mahavidyalaya, Nashik, Maharashtra, India

⁴Professor and HOD Department of Panchakarma, National Institute of Ayurveda Deemed to be University, Jaipur, Rajasthan, India

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INTRODUCTION

As the virus evolves with different mutations, causing an increasing number of infection hotspots around the world, the COVID-19 related pandemic is posing unexpected issues in public health. There has been increasing reports of multisystem inflammatory syndrome (MIS) associated with this pandemic. And lot of theories and possible causes of association of MIS with this pandemic along with treatment protocol is still evolving. Immunity has its significance in the pathogenesis of COVID-

19 irrespective of its severity. In the early-stage lesser tissue damage and considerably low inflammatory manifestations may be effect of strong immune response which must be competent of restricting viral entry, inhibiting viral replication and to purge the host's infected cells. During later stage, strong cell-mediated immune response with cytokine storm can be a factor responsible for critical manifestations. Cytokine Storm Syndrome are a group of disorders representing a range of inflammatory etiologies leading to devastating systemic inflammation, hemodynamic instability, multiple organ dysfunction, and potentially loss of life [1].

Children with primary COVID-19 reported to develop a life-threatening hyper-inflammatory state 4–6 weeks after primary infection called as Multisystem Inflammatory Syndrome in Children (MIS-C), Clinical features in children have varied but predominantly include shock, cardiac dysfunction, abdominal pain, and elevated inflammatory markers, including C-reactive protein (CRP), ferritin, D-dimer, and interleukin-6 [2]. Similar evidences have also been reported in adults (MIS-A) [3]. In addition, pre-existence of NCDs in COVID-19 patients could intensify and worsen the inflammatory pathology and increase the mortality risk [4].

Pathogenesis of post COVID-19 Syndrome

The receptor for the virus SARS-CoV-2 is a protein called ACE2 receptor, Expression of ACE2 reveals the multifaceted nature of COVID-19 infection [5]. Higher the ACE2 expression (or level) is, the higher the risk [6]. In recent study patients with comorbidities showed higher ACE2 expression as compared to control, again underlying disease may have more imbalanced RAS homeostasis, lower immunity and greater susceptibility to SARS-CoV-2 [7].

Endothelial cell infection by a virus causes damage, inflammation, and dysfunction in vessels. However, it is likely that thrombosis in micro vessels of Covid-19 cases is because of immunothrombosis. Thus, a scarce innate immune response is a critical task in the pathogenesis of COVID-19 Again, a delayed and insufficient IFN-I response to the virus allows viral imitation and increased oxidative stress, which leads to excessive inflammation, coagulopathy, and worsening hypoxia as a result of the NF-B-driven cytokine storm [8]. In the severe cases there is a vital role of oxidative stress and pro-inflammatory NETs and tissue injury [9]. In short, inflammation can be elucidated as a retort of living tissue towards injury. Acute inflammation is associated with fever and leukocytosis [10]. Metabolic syndromes among chronic disease category are strongly associated with chronic inflammation [11]. Chronic inflammation has been revealed as the main source of most lung fibrosis processes and may perhaps lead to epithelial damage and fibroblast activation [12]. Old people are more likely to have fibrosis due to immunosenescence [13]. As per some studies previous comorbidities are linked with severity and the severity of COVID-19 is also related to the rigorousness of post-COVID-19 expressions [14]. Treatment approach is thought to aim at reducing the net ROS levels and NET formation [15]. Siddiqi et al. proposed the use of immunomodulatory therapies in the state of hyperinflammation in COVID-19 stage before multisystem organic damage occurs [16]. The target during the early and later stage should be to squeeze viral propagation and to reduce the inflammatory response of the immune system respectively. Some Anti-inflammatory drugs and interleukins found to reduce Cytokine storm [17].

COVID-19 has shared pathology with *Agantuj shotha Vyadhi* of Ayurveda

Ayurveda a traditional system of Medicine also called as 'science of life' with its holistic approach involves the use of potent herbal leads to eliminate the root cause of the disease by restoring balance, at the same time creating a healthy life-style to prevent the recurrence of imbalance. In Ayurveda inflammatory responses are elaborated under terminology of *Shotha* which is again classified in two groups depending on causative factors known as *Nija* (endogenous) and *Agantuja* (exogenous) [18]. Communicable diseases are categorized under *Agantuja* (Exogenous) *Vyadhi* [19]. *Agantuj Vyadhi* ultimately represents itself as *Nija* (Endogenous) *Vyadhi* due to further vitiation of *dosha* and if vitiation is already there then *Agantuj vikara* can cause bigger threats [20]. Considering contemporary

pathophysiology and causative factor Sars CoV 2 virus which is exogenous in nature can be correlated with *Agantuj Shotha* (inflammation due to exogenous cause) [21]. again vitiated *Vata dosha* is linked with all types of Shotha, older age group, and chronic metabolic disorders [22–24]. *Vata Dosha* is supposed to administer the functions of nervous and musculo-skeletal systems and at the cellular level, associated with signaling pathways regulating cell growth, differentiation, and cell death [25].

Ayurveda approaches towards Infectious diseases.

Ayurvedic formulations/ treatment protocols attempt to correct metabolic defects and re-establish normal tissue functions (“*Dhatu Samya*”) with holistic approach [26]. *Rasayana* (rejuvenation therapy), a branch of Ayurveda, dedicated to achieve prolong life and prevent aging by nourishing all *Dhatus* (tissue elements) and reducing degenerative processes, prevent diseases by restoring the basic homeostatic balance and to promote excellent health and wellbeing [27]. It toned up the body to fight when exposed to adverse conditions and enhance different body defense mechanisms so as one can easily get adapted to different types of adverse situations [28]. Most of *Rasayana* formulations are available in *Avaleha* form; which seems to be analogous with mucoadhesive drug delivery system intending to provide better drug absorption through the oral cavity [29, 30] along with prolongation of therapeutic effects, bioavailability enhancement, cost-effective and improved patient compliance [31]. We found *Kamsahareetki* a polyherbal formulation for group of indications as given in Figure 1. to be one of the most apposite formulations [32].

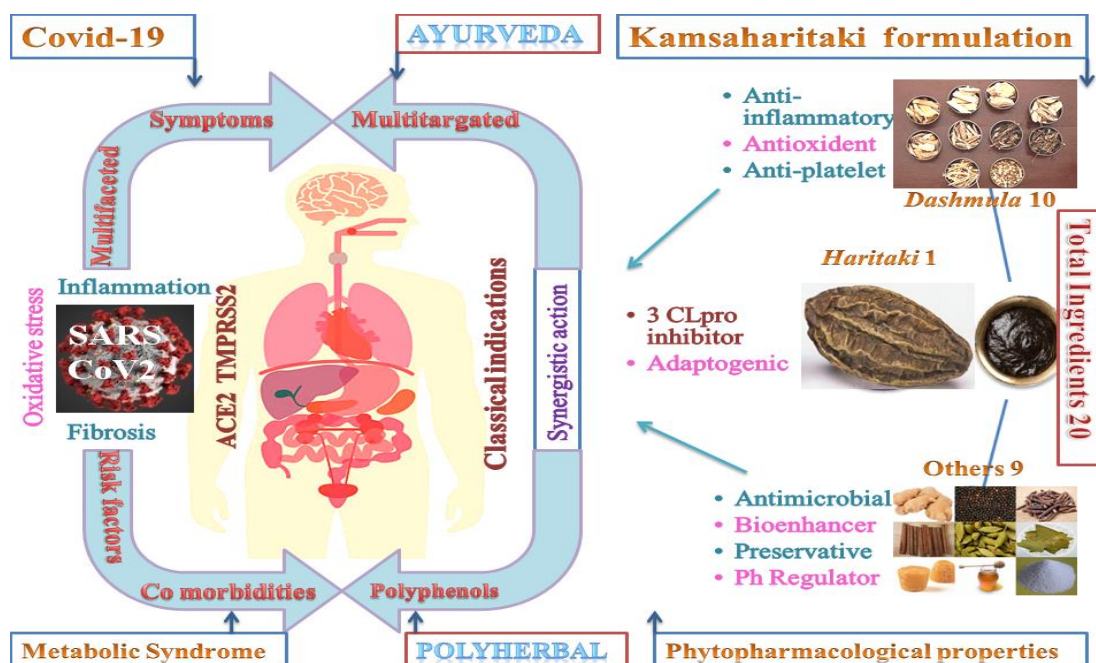


Figure 1. Graphical abstract.

METHODOLOGY

A keen exploration of *in vitro*, *in vivo* studies with electronically published data limited to Pubmed search engine interrelated to phytochemicals and pharmacological properties of each solitary herb of *Kamsaharitaki* formulation along with predefined groups of herbs constituting this formulation is carried out. Search source was altered to google scholar for one ingredient ‘*Kshara*’ on the basis of no results found in Pubmed search engine.

This traditional formulation is a composite mixture consisting of different active phytocompounds with very wide range of biological properties effective on different targets. In such a complex formulation, it is very tough to elucidate the mechanism of actions. Furthermore, in this type, the synergistic or antagonistic properties of compounds are not easy to deal with on the basis of current

scientific validations. But we have tried our best to identify potential of each element of this formulation on the basis of classical Ayurvedic texts and current scientific validations as described in Table 1. With the current available data contents of this formulations with their scientific nomenclature is given in Table 2 [33].

Table 1. Phytochemical and pharmacological potentials of *Kamsaharitaki* ingredients.

S.N	Scientific Name	Phytochemical constituents	Properties
1	<i>Aegle marmelos</i> Corr.	Marmin, marmesin, umbelliferine and skimmianine [34].	anti-inflammatory, antioxidant [35]
2	<i>Premna integrifolia</i> Linn.	iridoid glycosides, alkaloids, flavonoids and phenolic compounds [36]	analgesic/antinociceptive, anti-arthritic, antibacterial, antitumor, anti-inflammatory, antimicrobial, hypolipidemic, antioxidant, antiparasitic, antiulcer/gastro-protective, cardioprotective, CNS depressant, hepatoprotective, hypoglycemic, immunomodulatory, longevity-promoting and neuroprotective, antihistaminic, antikinase, COX-inhibitory [37]
3	<i>Oroxylum indicum</i> Vent.	baicalein, chrysin, and oxoxylin A [38]	antioxidant, antidiabetic, anti-adipogenesis, hepatoprotective, and anti-inflammatory activities [39]
4	<i>Stereospermum suaveolens</i> DC.	-sitosterol, n-triacontanol, lapachol, dehydro—lapachone, and dehydroprotectol are flavone glycosides found in root heart wood. Dinatin, dinatin-7-glucuronide, dinatin 7-glucuronide, quinones, stereochoenols A and B, naphthoquinones, stereokunthol B and stereokinone C, stereolensin, p-coumaric acid, palmitic, stearic, and oleic acids, and Cycloolivil [40]	antimicrobial, antiprotozoal and anti-inflammatory [41]
5	<i>Gmelina arborea</i> Linn.	flavonoids (apigenin), phenolics [42]	anti-inflammatory and anti-nociceptive, antioxidant, immunomodulatory [43]
6	<i>Solanum indicum</i> Linn.	alkaloids, saponins, flavonoids, glycosides, terpenoids, and steroids [44]	Antipyretic [45]
7	<i>Solanum xanthocarpum</i> Schrad. and Wendl.	flavonoids, alkaloids, sterols, and various glycosides, saponins, high levels of coumarins, in particular of scopoletin and esculetin [46]	antioxidants and antitumor, antidiabetic, anti-fungal, anti-psoriatic, anti-bacterial, antinociceptive, antileishmanial, mosquito larvicidal, molluscicidal, asthmatic, hepatoprotective, diuretic, nephrotoxicity, antiurolithiatic and antiplatelet activity [47]
8	<i>Desmodium gangaticum</i> DC.	pterocarpinoids, gangetin, gangetinin and desmodin	antioxidant, cardioprotective [48]
9	<i>Uraria picta</i> Desv.	Trace of alkaloid [49]	analgesic, anti-inflammatory, antioxidant, aphrodisiacs, and fracture-healing properties [50, 51]
10	<i>Tribulus terrestris</i> Linn.	saponins, polyphenolic compounds, and alkaloids. The steroidal saponins are chiefly furostanol and spirostanol variety, Harman, harmine, and harmalol of The β -Carboline indole alkaloid group, terrestrosin D, tribulusamide D, 70 different compounds have been identified till date [52]	anti-inflammatory, antioxidant, antifibrotic [53, 54]
11	<i>Terminalia chebula</i> Retz.	tannins of <i>T. chebula</i> fruit are of pyrogallol (hydrolysable) type and	Antioxidant, Antibacterial, Antifungal, Antiviral, Antiprotozoal, Anticarcinogenic, Radioprotective,

		Juang L J et al. gallic acid, neochebulinic acid, chebulagic acid, punicalagin, chebulanin, corilagin, ellagic acid, chebulinic acid, 1,6-di-o-galloyl-D-glucose, casuarinin, 3,4,6-tri-o-glloyl-D-glucose, terchebulin, 1,2,3,4,6-penta [55].	Antimutagenic, Chemopreventive, Hepatoprotective, Cardioprotective, Cytoprotective, Antidiabetic, Renoprotective, Antiinflammatory, Antiarthritic, Adaptogenic, Antianaphylactic, Hypolipidemic, Hypocholesterolemic, Gastrointestinal motility, Antiulcer, Antispasmodic, Anticaries, Wound healing, Purgative, Antiallergic and most importantly Immunomodulatory [56].
12	Jaggery	Phenol and phenolic acids [57].	Cytoprotective, DPPH radical scaving activity [58].
13	<i>Piper longum</i> Linn.	Piperine [59].	Bioenhancer [60].
14	<i>Piper nigrum</i> Linn.	Piperine [61].	bioenhancer [62]
15	<i>Zinziber officinale</i> Roxb.	gingerols, paradols and shogaols, polysaccharides, lipids, organic acids, and raw fibers [63].	antioxidant, anti-inflammatory and Improves glucose tolerance [64].
16	<i>Cinnamomum Zelynacum</i> Blume.	Cinnamaldehyde [65].	Hypoglycemic, Immunostimulant, ACE inhibitor [66,67].
17	<i>Elettaria cardamomum</i> Maton.	Volatile Phenolic Compounds [68].	anthyperlipidemic, hepatoprotective, antioxidant [69].
18	<i>Cinnamomum tamala</i> Ness		antidiabetic, antihyperlipidemic and antioxidant [70].
19	Potassium carbonate (alkali prepared with <i>Hordeum vulgare</i> Linn.)	chloride, Sulphate, Nitrate, Potassium, calcium, Iron, Magnesium [71]	alkalizer, dehydrating agent [72].
20	Honey	Multifaceted phenolic fractions [73].	antioxidant, antimutagenic, immune regulatory, anti-inflammatory, and estrogenic responses [74].

Table 2. Kamsaharitaki formulation

S.N	Name	Scientific Name	Quantity
1	Bilva	<i>Aegal marmelos</i> Corr.	300Gm
2	Agnimantha	<i>Premna integrifolia</i> Linn.	300Gm
3	Shyonaka	<i>Oxoxylum indicum</i> Vent.	300Gm
4	Patala	<i>Stereospermum suaveolens</i> DC.	300Gm
5	Kashmari	<i>Gmelina arborea</i> Linn.	300Gm
6	Brihati	<i>Solanum indicum</i> Linn.	300Gm
7	Kantakari	<i>Solanum xanthocarpum</i> Schrad. and Wendl.	300Gm
8	Shaliparni	<i>Desmodium gangaticum</i> DC.	300Gm
9	Prishniparni	<i>Uraria picta</i> Desv.	300Gm
10	Gokshuru	<i>Tribulus terrestris</i> Linn.	300Gm
11	Haritaki	<i>Terminalia chebula</i> Retz.	150gm
12	PuranaGuda	Jaggery	500Gm
13	Pippali	<i>Piper longum</i> Linn.	66Gm
14	Marich	<i>Piper nigrum</i> Linn.	66Gm
15	Shunthi	<i>Zinziber officinale</i> Roxb.	66Gm
16	Twak	<i>Cinnamomum Zelynacum</i> Blume.	33Gm
17	Ela	<i>Elettaria cardamomum</i> Maton.	33Gm
18	Talishpatra	<i>Cinnamomum tamala</i> Ness	33Gm
19	Yavakshara	Potassium carbonate (alkali prepared with <i>Hordeum vulgare</i> Linn.)	23Gm

20	<i>Madhu</i>	Honey	375Gm
21	<i>Jala</i>	Water	24 Ltr

*All values are approximately imitative with Ayurvedic parameters.

Dashmula: First ten herbs mentioned in *Kamsaharitaki* formulation Table 2 are collectively called as *Dashmula*, which found likely to possess the similar mechanism of action as aspirin i.e., prostaglandin inhibition. Similarly Undiluted *Dashmula decoction* showed inhibition of ADP ($P < 0.01$) and collagen ($P < 0.05$) induced platelet aggregation [75].

Terminalia chebula Retz. This fruit was given to animals for evaluation of their adaptogenic potential. All of them were able to aid the animals against a variety of different stressors working in various ways [76]. Upadhyay S et al proposed prospective therapeutic potential of the aqueous extracts of *Haritaki* (*T. chebula*) against SARS-CoV-2 based on 3CL^{pro} protease activity inhibition [77]. *T. chebula* extract furthermore target HSV-2 glycoproteins which are accountable for its binding to host cell receptors [78].

Jaggery, if *T. chebula* is consumed with *Jaggery* it gives benefits in all types diseases [79]. Some experimental studies showed lung tissue protective activity against coal and silica [80].

Piper nigrum Linn., *Piper longum* Linn and *Zingiber officinale* Roxb. These three herbs collectively called as **Trikatu** which acts as bioenhancer. The bioenhancer has multiple benefits as reduced drug dosage, cost effectiveness and reduced rate of drug resistance and lesser risk of adverse drug reaction [81].

Cinnamomum zeylanicum Blume, *Elettaria cardamomum* Maton, and *Cinnamomum tamala* Ness collectively called as **Trijata** or *Trisugandhi* (aromatic compound), these are rich in volatile oil and may possibly acts as bioenhancer with shelflife improvement [82].

Yava Kshara – (alkali prepared with barley – *Hordeum vulgare*), *Kshara* possibly be used as Ayurvedic alkalizer to maintain acid base homeostasis [83]. *Kshara* exert corroding and dehydrating action and are therapeutically used for drying excess fluidity or vitiated *kapha*, reduction of mass or lump, and in various other conditions [84]. This gives dual benefits by acting on disease as well as natural additive for pH regulation in formulation.

Honey is supposed to interfere with several targets in cell signaling pathways. On the other hand Honey plays a crucial role on pharmacokinetics of drug [85]. And with antimicrobial action it acts as potent natural preservative.

Figure 2 shared targets of *Kamsaharitaki* and COVID-19.

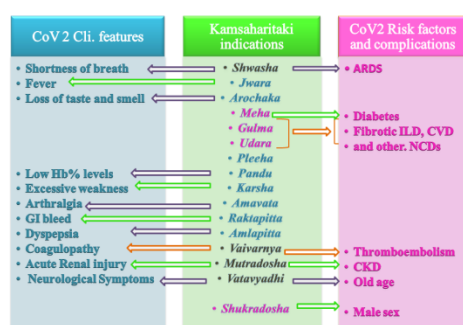


Figure 2. Kamsaharitaki and COVID.

Kamsaharitaki for Post CoV2 syndrome.

Kamsaharitaki is indicated in total 17 different conditions can be grouped up on the basis of their possible resemblance with CoV2 Clinical features, Risk factors, co morbidities and Post CoV2 complications. An inflammatory condition (*Shotha roga*) is primary indication of this formulation. Significance of inflammation associated with CoV2 is very well discussed earlier. Furthermore, the coexistence of noncommunicable chronic diseases (NCDs) in COVID-19 patients may intensify and worsen the inflammatory pathology and increase the risk for adverse outcomes and mortality [86]. Hence prompt commencement of the anti-inflammatory therapy is likely to attain a positive treatment response [87]. In Ayurveda, various diseases of several organ systems are illustrated under the single roof of *Shotha* on the basis of inflammation as common factor [88]. Other indications and their possible relation with CoV2 are shown in Figure 1. which seems to be analogous with increased inflammatory profile in Metabolic syndrome [89]. Among them are:

Gulma is an important phrase to understand since it describes a situation in which a mass of cells forms within the Thoraco-abdominal cavity Internal tumours or growths, including phantom tumours, are referred to as Gulma. Between the extreme confines of the heart's (Hriday) and bladder's (Hriday) regions on the inside of the body (Vasti) [90]. Researchers suggested that both *Gulma* and *Udara* are to be taken to understand abdominal malignant tumours in Ayurvedic context [91]. Fibrosis is a condition in which extra connective tissue forms, leading stromal hardness and scar development. Desmoplasia is a term that refers to the formation of benign fibrous tissue in response to tissue harm such as infection or malignancy [92]. Similarly *Gulma* represents hard (*Kathinibhuta*), densely elevated tissue (*Kundalibhuta-Mansadyuttundnena*) comprising either organs like Heart (*Hriday*), Bladder and surrounding area (*Basti*), Both lateral sides of thorax (*Parshwa*) and Umbilical region (*Nabhi*) with mild to moderate varying intensity of pain, secondary to several diseases and metabolic abnormalities [93]. *Vagbhata* states that there are etiological similarities among CVD (*Hridroga*) and *Gulma* [94]. With the help of this *Gulma* can be considered in terms of fibrosis, scar or abdominal adhesions like Cardiorenal fibrosis, fibrotic interstitial lung disease (ILD) and other similar manifestations which are again akin to complications associated with COVID-19 [95].

Figure 3, *Kamsaharitaki* indications are analogous with ACE2 and TMPRESS2 expression.

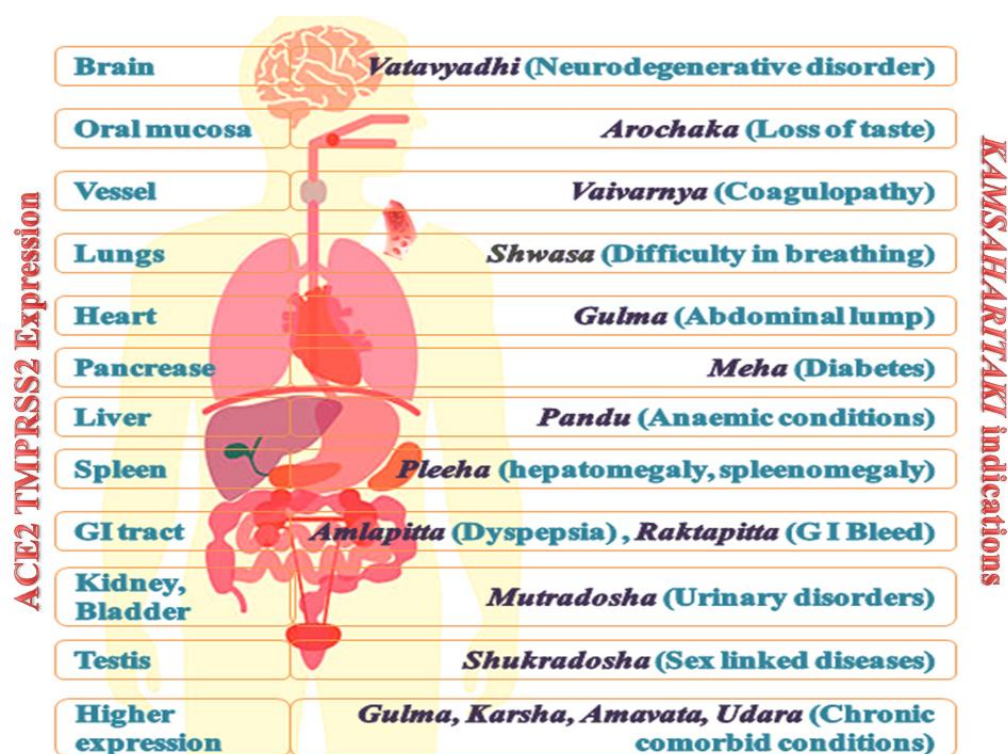


Figure 3. *Kamsaharitaki* Indications

DISCUSSION

Several components of Kamsaharitaki include anti-inflammatory, anti-platelet, and antioxidant properties that may be useful in decreasing the cytokine storm, making this a potentially successful therapy option. Chief constituent of this formulation *T. chebula* possess potential of 3CL^{pro} protease activity inhibition which is eye-catching therapeutic target for SARS-CoV-2.

As reactive oxygen species produced (ROS are composed of many species, such as, oxygen ions, peroxides, hydroxyl radicals, etc.; to quench them a combination of antioxidants is required. Plant polyphenolics though are good source, but they may be at variance in their abilities to quench distinct species of ROS therefore, combination of phytochemicals is extremely recommended [96].

Some of the pharmacological actions of active constituents of plants are significant only when these are potentiated by other plants, but not apparent when used single-handedly. This event of positive herb-herb interaction is known as Synergism [97].

Whole plant decoction is used in this formulation; it may exhibit improved bioavailability and lower toxicity than single chemical entity. On a concise note action of ingredients of this formulation possess desired therapeutic potential properties against multisystem inflammatory syndrome with bioenhancers and natural additives to improve taste, absorption and reduced damage while storage.

Kamsaharitaki is primarily indicated in inflammatory conditions and other group of indications which shows relative connection with metabolic syndrome, known to be major risk factor for COVID-19. Therapeutic indications of *kamsaharitaki* formulation have close resemblance with clinical features of COVID-19.

Post COVID-19 fibrotic changes and tissue damage seems to be akin with indications of *Kamsaharitaki* and combination of several polyphenolics with antioxidant property may play crucial role in tissue repair. ACE2 and TMPRSS2 expression cites and *Kamsaharitaki* indications are also analogous to each other.

CONCLUSION

With the help of phytopharmacological exploration we can conclude that, ingredients of *Kamsaharitaki* formulation possess diverse phenolic compounds with Antioxidant, anti-inflammatory, antithrombolytic, anti-ageing, adaptogenic, immune-modulating properties along with 3CL^{pro} inhibitory potential; on the basis of potential evidences further research on synergistic mechanism of this formulation for combating COVID-19 clinical manifestations, restraining cytokine risk and preventing and reversing post CoV 2 fibrotic lesions may promisingly be carried out.

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