Review Article

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A CRITICAL REVIEW OF JWARAHARA YOGAS OF AYURVEDIC CLASSICS: A PARADIGM TO REVERSE PHARMACOLOGY

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ABSTRACT

Jwara is the first and foremost among all somatic diseases. Although an independent disease, it is also seen manifested in the form of premonitory symptom, symptom and causative factor of various disorders. 2019-20 has witnessed a new pandemic identified as Corona virus (COVID-19) with adverse health issues. In proportion to the wide variety of diseases, viral vaccines are very few, that too with adverse effects. Hence there is an urgent need of most promising Indigenous drugs with antipyretic and anti-viral activity in the current scenario. A critical analysis is made to explore the Jwarahara Yogas of classics to unfold the Antiviral, Antipyretic, Antioxidant and Immunomodulatory potential of phytochemicals in formulations. An attempt has been made to explore the antiviral and antipyretic potential of Amrutotharam Kashayam, one of the most popular and widely used Jwarahara yoga in classics. The review will definitely give new insights on the synergistic actions of phytochemicals in formulations to revalidate the clinical evidences and will throw lime light on repurposing of the documented novel drugs and combinations in classics to offer unique preventive strategies and therapeutic solutions to the present pandemic and emerging viral infections.

Keywords: Jwara, Jwarahara Yogas, Antipyretic, Antiviral, Phytochemicals, Formulation.

INTRODUCTION

Ayurveda has a different and unique outlook on treatment modality of multifactorial disease entities with varied symptoms. The novel concept of samyoga/combination of herbs and their multi targeted mode of action is evident in the compendiums of Ayurveda. The phytochemicals from plants have been broadly studied for their antipyretic and antiviral activity. But the mechanisms by which poly herbal drugs and their extracts act differ in many respects from the actions of single substances or synthetic drugs[1]. In fact, Jwarahara Yogas of classics are designed in a unique way that the anti-inflammatory, anti-viral, anti-pyretic, antioxidant, immunomodulatory potentials of drugs act in synergy to enhance the body's overall natural resistance to the disease-causing agent rather than directly neutralizing the agent itself. Validation of Ayurvedic drugs with reverse pharmacology is the need of the hour.

Jwara is a disease entity which simultaneously afflicts the body, mind and sense organs[2]. Jwara is classified into various types based on Doshik predominance, caused by internal or external factors in the classical text books of Ayurveda. Indulgence in improper diet and regimen vitiates the tridoshas which in turn hampers agni, obstructs the channels of rasa and sweda and expels agni (Digestive and Metabolic factors) from its site to different parts of the body resulting in elevation of body temperature[3]. Nidana Parivarjana (eliminating the root cause) is the first line of treatment in any disease. While explaining the treatment of Jwara, Acharyas clearly explain to avoid factors which aggravate Doshas, specifically Pitta Dosha.

A thorough analysis of classics reveals that the fundamental principle of combating any form of Jwara is digesting the ama, preserving the agni, relieving Shrotorodha (Obstructive pathology occurring in channels) and inducing sweat which inturn brings down the temperature.

The commonly used potent Kashayas (decoctions) & Gutikas (tablets) mentioned under Jwara chikitsa are compiled (Table 1 & 2) and analyzed by identifying the exact phytochemicals responsible for the definite pharmacological action of the drugs to revalidate the rationale of adopting these formulations in Jwara chikitsa. 10 Jwarahara Kashaya Yogas and 10 Gutika Yogas of poly herbal and herbo-mineral combination with remarkable therapeutic efficacy is enlisted from among the wide yet diverse group of formulations.

Probable Mode of Action

In Ayurveda, the mechanism of action of drug can be explained in terms of Rasa Panchaka viz; Rasa (taste), Guna (property), Virya (potency), Vipaka (Biotransformation of Rasa) and Prabhava (Exceptional action). On analyzing the formulations, it was observed that each formulation is unique in its own way due to its Rasa Panchaka and Dosha karma (action on vitiated doshas) capable enough to break the Samprapti (pathogenesis) of Jwara.

Table 1: List of Kashaya Yogas with Phytochemicals and its Action

Ingredients	Phytochemicals		Specific pharmacological actions
	Antipyretic	**Antiviral**	
1. Amrutotharam Kashaya (Sahasrayogam- Jwara prakarana)			
Heart leaved Moonseed (*Tinospora cordifolia*)	Flavonoid, Diterpenoid, Alkaloid, Berberin	Tinosporin[4]	Anti-pyretic
Ink nut (*Terminalia chebula*)	Flavonoids[6]	Chebulagic acid[5] Gallic acid Galloy glucoses Chebulinic acid	Antiviral activity
Dry ginger (*Zingiber officinale*)	Gingerol	Quercetin[7]	Anti-viral activity
		B-Sesquiphellandrene[8]	Anti-rhino-viral activity
		Allicin[9]	Anti-influenza
		Ingenol[10]	Anti-viral activity
		6-shogoals[10]	Anti-viral activity
2. Shadanga paneeya – Jwara Chikitsa – A.H.Chi.1/15			
Nut grass (*Cyperus rotundus*)	Quercetin[11]	Quercetin	Anti-pyretic activity, Anti-DENV-2[12] Inhibitory activities, Influenza infection[13]
	Sequesturpenoids	Sequesturpenoids	Anti-HBV activity
	β-Sitosterol	_	Antipyretic activity[14]
Sandalwood (*Santalum album*)	_	β-santalols[15]	Anti-influenza A/HK (H3N2) virus activity
		α- santalols[15]	
Cuscus grass (*Vetiveria zizanioides*)	_	_	Antipyretic activity
Indian fumitory (*Fumaria parviflora*)	_	Narlumicine* Oxysanguinarine* β-Sitosterol	Fumaria indica -DENV (Dengue Virus) inhibitor[16]
		Quercetin[17]	_
Dry ginger*			
Coleus**			
3. Pachana Kashaya AH.Chi.1/65-66			
Canchorie root plant (*Tragia involucrata*)	Tritrepenoid, Flavonoids, Tannins	_	Anti-pyretic activity[18]
Velvet leaf (*Cyclea peltata*)	_	Bebeerine*[19] (*Cissampelos pareira*)	Protection against DENV (Dengue Virus) infection*, Antipyretic activity[20]
Nut grass*/Fine leaf fumitory*/Dry ginger*/Cuscus grass*/Coleus*			
4. Pachana Kashaya (b) AH.Chi.1/65-66			
Green chiretta (*Andrographis paniculata*)	_	Andrographolide neoandrographolide 14-deoxy-11,12-didehydroandrographolide	Viricidal activity[21] against herpes simplex virus 1 (HSV-1) Antipyretic activity[22]
Heart leaved Moonseed*/Nut grass*/Dry ginger*			
5. Guduchyadi gana Kashaya Ashtanga Hridaya sutra 15/16			
Neem (*Azadirachta indica*)	Nimbidin	Flavonoids, Triterpenoids Glycosides, Beta-pinene limonene	Antipyretic action[23]- In hyper pyretic rabbits Antiviral action[24] - action coxsackie B
Coriander (*Coriandrum sativum*)	_	Beta-pinene& limonene [25]	Antiviral activity against herpes simplex virus type 1 (HSV-1) *in vitro*
Red sandalwood (*Pterocarpus santalinus*)	Flavonoids	_	Antipyretic activity[26]
Orris root */ Heart leaved Moonseed *			
Wild Himalayan cherry (*Prunus cerasoides*)- Antioxidant**			
6. Nimbadi kashaya Chakradutta, Jwara chikitsa :101			
Indian night shade (*Solanum ptychanthum*)	Flavonoids, Steroid Saponins, Anthraquinone, Tannins	Flavonoids Terpenoids lignans Sulphides Polyphenolics Coumarins	Antipyretic activity[27] Antiviral effects by inhibiting the formation of viral DNA or RNA
Long pepper – Pippali */ Neem */ Dry ginger*/ Heart leaved Moonseed */ Deodar */ King of bitters*			
Piper chaba/ Spiked ginger lily (*Hedychium spicatum*) - Antioxidant**			
7. Drakshadi kashaya A.H.1/55-58			
Grapes (*Vitis vinifera*)	_	Resveratrol (RV) [28]	Inhibit the *in vitro* and *In vivo* replication of influenza virus. *In vivo* anti-*Herpes simplex* virus activity, antiviral action against polyomavirus inhibition of *varicella-zoster* virus replication *in vitro* human immunodeficiency virus type 1 (HIV)
	Quercetin, Rutin, Kaempferol, Luteolin Phenolic acids	_	Antipyretic
Indian butter tree (*Madhuca indica*)	Flavonoid, Quercetin	_	Antipyretic [29]

Liquorice (*Glycyrrhiza glabra*)	_	Glycyrrhizin[30]	*Varicella-zoster* virus (VZV) *in vitro* RNA and DNA viruses, human immunodeficiency virus (HIV) infection. SARS (severe acute respiratory syndrome) virus, i.e., FFM-1 and FFM-2
	_	Glycyrrhizin, Licorice and Glycyrrhizic acid	*In vitro* antiviral activity on Japanese encephalitis virus against SARS−Coronavirus[31]
Lodh tree, (*Symplocos racemosa*)	Phenolic Glycoside[32] Alkaloids, Steroids	_	Antipyretic activity
Indian sarsaparilla (*Hemidesmus indicus*)	_	β-sitosterol[33]	Antipyretic activity
Indian gooseberry (*Phyllanthus emblica*)	_	Ascorbic acid	HIV infection[34]
		Gallic acid, Ellagic acid, Tannins and Catechins	Anti-HIV-1 activity, HSV[34]
		1246TGG[35] (1,2,4,6-Tetra-O-galloyl-beta-D-glucose)	Anti-HSV activity
Indian lotus (*Nelumbo nucifera*)	Flavonoids, Glycosides, Kaempferol derivatives Nelumboroside A and B 2. Isorhamnetin glycosides 3-O-β-D-glucopyranoside, Isorhamnetin 3-O-a-L-Rhamnopyranosyl-(1→6) -β -D-glucopyranoside	(+)-1(R)-coclaurine, (–)-1(S)- Norcoclaurine and Quercetin	Antipyretic activity[36] Anti-HIV activity[37]
Blue lotus (*Nelumbo nucifera*)	Nymphayol[38]	_	Antipyretic
Ceylondate palm (*Grewia asiatica*)	_	_	Antipyretic activity[39] Antiviral
Sandalwood* /Nutgrass* /Coleus*/Gmelina*/Lotus*/Wild Himalayan cherry*/Cuscus grass*			
8. Panchatikta Kashaya			
Febrifuge plant (*Solanum xanthocarpum*)	_	Flavonoids[40]	Anti-Viral activity
Dry ginger (*Zingiber officinale*) * /Heart leaved Moonseed (*Tinospora cordifolia*) */Green chiretta (*Andrographis paniculata*) */ Orris root (*Inula racemosa*) - Antioxidant			
9. Indukantam kashaya (Sahasrayogam)			
Stone apple (*Aegle marmelos*)	Skimmianine[41]	Marmelide[41]	Anti-viral property against *Herpes Simplex* Type 1, Inhibition on HIV-1 entry and HIV-protease
Indian Elm (*Caesalpinia crista*)	_	Betulinic acid[42]	Anti-viral property against *Herpes Simplex* Type 1, Inhibition on HIV-1 entry and HIV-protease
		Betulin[43]	Anti-viral
Indian trumpet flower (*Oroxylum indicum*)	Flavonoids[44]	_	Anti-Pyretic
Rose flower fragrant (*Stereospermum suaveolens*)	_	Lapachol[45] Apigenin[46]	Anti-Viral
Dabra (*Uraria picta*)	Terpenoid, Tannins[47]	Flavonoids[48]	Anti-Pyretic, Anti-Viral activity
Indian nightshade (*Solanum anguivi*) */Febrifuge plant (*Solanum xanthocarpum*) */Long pepper (*Piper longum*) * / Dry ginger (*Zingiber officinale*) *			
Devil's weed (*Tribulus terrestris*) (Antioxidant) /Long pepper (*Piper longum*) (immuno- modulatory) /Balinese long pepper (*Piper retrofractum*) (Antioxidant)/Ceylon leadwort (*Plumbago zeylanica*) (Antioxidant)/Deodar (*Cedrus deodara*) (Antioxidant)/ Arni (*Clerodendrum phlomidis*) (antioxidant)/Headache tree (*Gmelina arborea*) (immuno-modulatory)/Tick tree (*Desmodium gangeticum*) (Antioxidant) **			
10. Patoladi Kashaya A.H.Chi.1/65-66			
Bitter snake gourd (*Trichosanthes cucumerina*)	_	Triterpenoid alcohol Euphol[49]	Anti-Viral
		Coumarin[50]	Viral growth Inhibition
Indian gooseberry (*Phyllanthus emblica*)	`Flavonoids[51]	_	Anti-Pyretic, Prostaglandin synthesis inhibitor
	-	Pentagalloylglucose[52]	Inhibit influenza
Hellebore (*Picrorhiza kurroa*)	-	Aungmaygaoside D (4), Sylvestroside IV dimethyl acetal (7), Sweroside (8)[53]	Viral protein R inhibitors
Ink nut (*Terminalia chebula*) */ Dry ginger (*Zingiber officinale*) */ Orris root (*Inula racemosa*) */ Heart leaved Moonseed (*Tinospora cordifolia*) */ Febrifuge plant (*Solanum xanthocarpum*) */Neem (*Azadirachta indica*) *			
Beleric myrobalan (*Terminalia bellerica*) (Antioxidant) **			

Table 2: List of Tablets with its phytochemicals and its action

Ingredients	Phytochemicals		Specific pharmacological actions
	Antipyretic	Antiviral	
1. Tribhuvanakeerti rasa (Yoga Ratnakara)			
Aconite (*Aconitum ferox*)	_	Hypaconitine Songorine, Mesaconitine Aconitine[54]	Alkaloids against tobacco mosaic virus (TMV) and cucumber mosaic virus (CMV).
Black pepper (*Piper nigrum*)	Alkaloid Piperine (trans isomer of 1-piperoyl piperidine[55]	Piperamides[56]	Antipyretic activity-yeast induced pyrexia in mice.
			Antiviral activity - inhibit coxsackie virus type B3 (CVB3).
Liquid media used for trituration: Juicy extract of leaves of Holy basil *(Ocimum tenuiflorum)*	_	Terpenoid[57]	Antipyretic activity- Tested in typhoid-paratyphoid A/B vaccine-induced pyrexia in rats.
Extract of leaves of White thorn apple (*Datura metal)*	_	Atropine[58]	Antiviral activity against herpes simplex virus, influenza virus
Purified cinnabar*/ purified borax*/ long pepper*/ extract of Ginger rhizome *			
2. Mrityuinjaya rasa (Bhaishajya Ratnavali Jwara Rogadhikara)			
	_	_	Antiviral activity- against H9N2 virus[59]
Darada / Cinnabar HgS	_	_	Antiviral activity[60]
Tankana /Borax $Na_2B_4O_7$. 10 H_2O	_	_	Antidote activity profile against Aconite[61]
Vatsanabha*/ Maricha*/ Kana*			
3. Anandabhairava rasa (Rasendra sara sangraha-Jwaradhikara)			
Nut meg (*Myristica fragrans*)	_	Terpenoids like sabinene, Myristicin and Eugenol[62]	*In vitro* anti-rotavirus activity
Lemon juice (*Citrus lemon*)	_	Hesperidin and Vitamin C[63]	Counteract the cell infection by **SARS-CoV-2** -reduce viral pathogenicity of NDV Newcastle Disease Virus
Hingula /cinnabar*/Tankana/Borax*/Monkshood* *Aconitum ferox* /Long pepper * *Piper longum* /Black pepper * *Piper nigrum* / Dry ginger*			
4. Hinguleswara rasa (Bhaishajya Ratnavali Jwara Adhikara)			
Long pepper*/Cinnabar*/Monkshood*			
5. Rasa Manikya (Siddha bhaishajya manimala-jwara prakarana)			
Arsenic tri- sulphide	AS_2S_3	_	_
6. Bilwadi gulika Ashtanga Hridaya Uttara 36/84-85			
Pongan oil tree (*Pongamia pinnata)*	Glycosides, Sterols Tannins	Adenine Arabinoside, Cytosine Idoxyuridine	Antipyretic activity in Brewer's yeast-induced pyrexia in rats.[64]
			Antiviral against HSV-1 and HSV-2[65]
Stinking cassia (*Senna tora)*	_	Flavonoids Emodinanthraquinone	Antiviral- anti-SARS-CoV activity[66]
Turmeric (*Curcuma longa)*	_	Curcumin, Gallium-curcumin, Cu-curcumin	Reduction of HSV-1 replication, anti-HIV[67]
Indian berry *(Berberis aristata)* Liquid media trituration: goat's urine	Alkaloids, Tannins, Terpenes, Resins, Phenols	Berberine[68]	Antipyretic
			Antiviral
Stone apple*/ Sacred basil*/ Deodar*/ Ink nut*/ myrobalan*/ Indian gooseberry *, / Long pepper*/ pepper*/ dry ginger*			
Beleric**			
7. Sudarshana choorna/Gutika Bhaishajya Ratnavali Jwaradhikara 308-317			
Sweet flag (*Acorus calamus*)	_	*β*.-asarone flavonoid	Antiviral action- HSV-1 and HSV-2.[69]
Persian manna plant (*Alhagi maurorum*)	Flavonoids, fatty acids, coumarins, glycosides, sterols, steroids.	_	Antipyretic[70]
Licorice (*Glycyrrhiza glabra*)	_	Glycyrrhizic acid	Antiviral activity- EV71, coxsackievirus A16
		Glycyrrhizin	Antiviral- hepatitis C
		Licorice, Triterpene	Antiviral
Drumstick (*Moringa oleifera)*	phenolics, flavonoids, tannins, saponins, terpenoids, isoquercetin glycosides such as niazirin, 4-hydroxymellein, β-sitosterol, and vanillin.	Flavonoid Tannin Saponin	Antipyretic[71] Antiviral
Asparagus (*Asparagus racemosus*)	Flavonoids Saponins	_	Antipyretic activity[72]

Cinnamom bark (*Cinnamomum verum)*	–	–	Antiviral activity against Influenza virus[73,] Parainfluenza and HSV 1 virus invitro.H1N1
Potash Alum	–	–	As adjuvant in F1-RSV vaccines increases viral clearance and Immunogenicity[74]
False calumba*/ turmeric*/ deodar*/ nut grass*/ Ink nut*/ Chinese pistache*/ febrifuge plant*/ dry ginger*/ Fine leaf fumitary* / Neem*/ Long pepper* / Coleus */ spiked ginger lilly*/ Orris root*/ root of long pepper */ False calumba*/ Turmeric*/ tree turmeric*/ Red sandalwood*/ wild Himalayan cherry*/ khaskhas grass*/ Ticktree* (*Desmodium gangeticum)*/ Ajwan* (*Trachyspermum ammi)*/ Atis* (*Aconitum heterophyllum)*/ stone apple*/ pepper*/ gooseberry*/ Heart leaved moonseed*/ Ceylon leadwort */ Ballon vine* (*Swertia chirata*) / Dabra* (*Uraria picta*)/ Bitter snake gourd* (*Trichosanthes dioica*)			
Indian gentian (*Gentiana kurroo)*/ Musk mellow (*Abel moschus moschatus*) / Stink vine (*Paederia foetida)* / 3 leaved pine (*Pinus roxburghii)*/ Frangipani vine / Conessi seeds (*Holarrhena antidysentrica)* (*Chonemorpha fragrans*)			
8. Vasantamalati rasa (Siddha bhaishajya manimala- Jwara prakarana)			
Gold bhasma (Gold-Au)	11% and 20% of Au[75]	–	Anti-pyretic
	–	Average size of 56–57 nm Au[76]	Inhibit Influenza virus
Purified cinnabar*/ Pepper*			
Pearl bhasma ($CaCO_3$) / Calamine/zinc ore (ZnO) / Butter / lemon juice (*Citrus lemon*)			
9. Vettumaran gulika (Sahasrayogam)			
Celery (*Apium graveolens*)	Flavonoids Alkaloids[77]	Thymol[78]	Anti-influenza, Anti-viral
		p-cymene[79]	Anti-viral, Herpes simplex virus Type 1
		γ-terpinene[79]	Anti-Viral
Blue vitriol	–	$CuSO_4$	Anti-Viral[80]
Realgar	–	As_2S_2	Anti-viral, Anti-HSV-2 activity[81]
Cinnabar*/ Borax*/ Black pepper*/ Indian aconite*/ Ginger juice*			
10. Chukkum tippalyadi gutika (Sahasrayoga Gutika prakarana -2)			
Indian aloe (*Aloe vera*)	Salicylic acid[82] β sitosterols Flavonoids[83]	–	Anti-Pyretic activity
Sweet flag (*Acorus calamus*)	–	b-Asarone[84]	Inhibit *Herpes simplex* virus HSV-1 and HSV-2 replication
Ballon wine (*Cardiospermum halicacabum*)	–	Flavonoids Phenolic acids[85]	Anti-Viral
Breast milk	–	Mucin[86]	Anti-poxvirus activity, Anti-HIV
Dry ginger*/ long pepper */ White cumin*/ Green chiretta*			
Cumin seed (*Cuminum cyminum*) / Woodenbegar (*Axis axis*) / Indian copaltree (*Veteria indica*) / Camphor (*Cinnamomum camphora*) / Civet cat secretion (*Viverra zibetha*)			

* drugs which are already specified in the table.
** the drugs which have antioxidant activity.
- specified activity not found.

Majority of the ingredients have tikta (bitter) as Pradhana rasa (primary taste) and Katu (pungent)/ kashaya (astringent) as anurasa (secondary taste). Among the Shadrasa's, tikta rasa possess Jwarahara property. It acts by virtue of its Deepana, Pachana and Lekhana property thereby ignites digestive fire, removes ama visha owing to its vishaghna nature (removes toxins), improves digestion, clear the rasavaha srotas (channels), improves taste, reduces daha (burning sensation), arochaka (anorexia) and subsequently alleviates pitta dosha & subsides Jwara (fever). Tikta-kashaya rasa, laghu-ruksha guna and sita virya of the combination helps in pacifying Kapha and pitta. Katu Vipaka does Pachana of doshas especially Kapha along with Pitta and stabilizes dhatwagni. The formulations were found to have sita virya and ushna virya dugs in which ushna virya induces Swedana, Ama Pachana, Deepana and removes Shrotorodha whereas sita virya mitigates pitta dosha.

According to Modern Pharmacology, the probable mode of action may be ascribed to the major groups of common plant secondary metabolites (SM) that produce a definite physiological action. The synergistic effects of these secondary metabolites may inhibit microorganisms and may interfere with metabolic processes or may modulate gene expressions and signal transduction pathways[87]. An attempt made to understand the diversity of SM and their modes of action, either alone or in combinations may contribute to the recorded pharmacological activities.

On analyzing the Jwarahara Kashaya Yogas (Table 1); we could enlist 16 drugs which possessed phytochemicals with demonstrated antipyretic activity whereas 23 ingredients had phytochemicals with antiviral potential against a variety of viruses. A total of 12 ingredients were found to exhibit both actions. Majority of the ingredients had profound immunomodulatory profile. Exploring the mechanisms of the antipyretic (Jwaraghna) action of the herbs in the formulation in Ayurveda thus involves antiviral, immunomodulatory and antioxidant potential of drugs working in synergy which will give a totally different perspective on treatment modality for fevers.

Analysis of Antipyretic activity

The essential elements of the fever physiologic pathway are release of pyrogenic cytokines by inflammatory cells in response to some exogenous pyrogen (e.g. infection), induction of cyclooxygenase (COX) 2 activation of the arachidonic acid cascade, and enhanced biosynthesis of prostaglandin E_2 (PGE_2) by hypothalamic vascular endothelial cells[88]. Through its effect on thermoregulatory neurons located in the preoptic area of the anterior hypothalamus, PGE_2 acts to raise the hypothalamic thermal set point and thereby induce peripheral and thermogenic mechanisms to increase core temperature. Antipyretic agents might interrupt the fever response at any step along this pathway.[89]

In majority of the drugs of the Yogas (Table 1 & 2) *In vitro* antipyretic activity effect in yeast provoked elevation of body temperature in rats comparable to that of paracetamol (standard drug) was established. Various researchers have claimed that the antipyretic effect of β-Sitosterol which is found in Musta (*Cyperus rotundus*) and Parpata (*Fumaria parviflora*) is comparable to that of aspirin. The antipyretic activity of various drugs may be attributed to the high content of flavonoids in drugs like Amrita (*Tinospora cordifolia*), Madhuka (*Madhuca indica*), Vacha (*Acorus calamus*), Rakta Chandana (*Pterocarpus santalinus*), Kamala (*Nelumbo nucifera*), Dunduka (*Oroxylum indicum*), Amalaki (*Phyllanthus embelica*), Draksha (*Vitis vinifera*), Haritaki (*Terminalia chebula*), Shatavari (*Asparagus racemosus*) etc. by inhibiting prostaglandin synthesis in hypothalamus. A study reported that Quercetin may inhibit fever causing inflammatory mediators[90]

In a recent study, the chemical analysis to ascertain the marker compounds of the Jwarahara Mahakashaya indicated the presence of flavonoids, which are well known for their antipyretic properties.[91]

In a nutshell, the antipyretic action of drugs may be interpreted as follows. β-Sitosterol block the pathway of phospholipase and inhibit the production of arachidonic acid. Flavonoids and its related compounds block the action of Cyclooxygenase pathway and inhibit the production prostaglandins (PGE2) thus reducing the fever[92].

Analysis of Antiviral activity

There are several mechanisms which govern the antiviral activity of phytochemicals. Few anti-viral phytochemicals, bind to carbohydrate moiety and tend to target the cell entry. These mechanisms will limit the viral attachment, penetration, coating, synthesis of proteins, assembly and release. Several *in silico* and *in vitro* studies have revealed the promising use of phytochemicals for the treatment of viral infections. A thorough analysis of Jwarahara property of drugs revealed astonishing antiviral potentials of phytochemicals (Table 1 & 2) and the mechanism of action of drugs can be illustrated in the following phases of viral life cycle.

Inhibition of viral attachment

6-Shogoals, 6-Gingerol, Allicin of Ginger blocks viral attachment and internalization. Tinosporin of Heart Leaved Moonseed inhibit the virus from establishing infection to target the t helper cells[93]. Glycyrrhizin**,** of licorice root does not allow the virus cell binding[94]. Mucin in breast milk binds and traps virus particles thus acts as artificial shield[86]. A recent study proposed that the benefit of hesperidin from citrus fruits may derive both from the binding to the coronavirus spike and from its anti-inflammatory activity[63]. Joshi *et al*. identified hesperidin among several natural molecules that strongly bind to SARS-CoV-2 main protease, and interestingly also to the viral receptor angiotensin-converting enzyme 2 (ACE-2).

Inhibition of virus entry

Quercetin, in plants like Musta (*Cyperus rotundus*), Shunthi (*Zingiber officinale*), Parpata (*Fumaria parviflora*) etc and Curcumin[103] in *Curcuma longa* exhibits initial phase of antiviral activity by interaction with viral surface glycoprotein (HA, hemagglutinin) and inhibition of virus entry into the cell.[95]

Inhibits uncoating or release of virus particles

Glycirrhin inhibits the penetration, uncoating or release of virus particles[96]. Eugenol in *Myristica fragrans* does direct inactivation of Virus particles[97]

Inhibition of RNA synthesis

β-santalols in Sandalwood (*Santalum album*) decreases viral mRNA synthesis[15]. Curcumin in *Curcuma longa* inhibits viral RNA, protein synthesis and virus titer[98].

Inhibits glycosylation of viral proteins

When the viral proteins are under-glycosylated there are chances of new virion formation but in the presence of Atropine the virions will remain non-infectious[104]. The Chemical Atropine which is present in *Datura metel* blocks the glycosylation of viral proteins. There will be reduction in production of infective viral particles. The Coumarin present in Bitter snake gourd (*Trichosanthes curcumerina*) inhibits viral growth[50].

Inhibition of Viral replication

The chemicals in Neem such as flavonoids, triterpenoids, glycoside, Beta-pinene limonene interfere at an early event of virus replication cycle[105]. Chebulagic acid and chebulinic acid in Haritaki (*T. chebula*) inhibits virus replication. Glycyrrhizic acid could inhibit the replication of coronavirus SARS *in vitro*[94]. β-Asarone of *Acorus calamus* prevents the replication of both HSV-1 and HSV-2[99]. Thymol in celery[100] and Eugenol may interact with viral envelope can cause damage to viral envelopes of freshly formed virions and can cause inhibition of viral replication at the initial stage[101] Glycyrrhizin is effective in controlling viral replication of SARS (severe acute respiratory syndrome) virus[102]

In this review, a humble attempt is made to explore the diverse plant secondary metabolites and explain their underlying modes of action to revalidate the time-tested evidences of our sacred science. In this regard, an attempt is made to analyse the probable mode of action of Jwarahara formulations citing Amrutotharam Kashayam, the most popular and potent yoga for treating Jwara as an example.

Probable Mode of Action of Amrutotharam Kashayam

Antipyretic activity (Figure 1)

The flavonoids present in *Tinospora cordifolia* (Amrita) are known to target prostaglandins which are involved in Pyrexia. Inhibiting central production of PGE_2 is a well-known mechanism of antipyretic agents but activated leukocytes and endothelial cells in peripheral areas of inflammation also represent potential drug target[106]. It appears that the flavonoids content of *Terminalia chebula* may be responsible for its antipyretic activity by inhibiting prostaglandin synthesis in hypothalamus[107] (Figure 1).

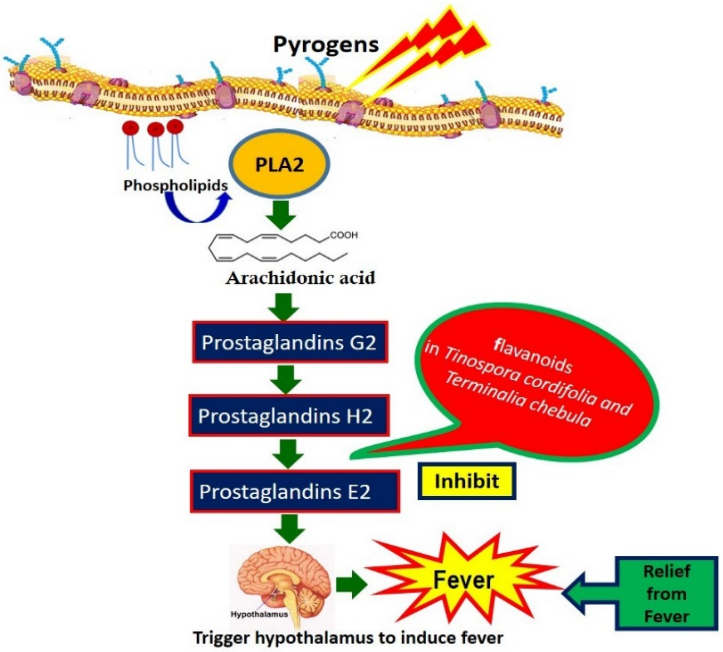

Figure 1: Probable Mechanism of Antipyretic Activity of Amrutotharam Kashayam

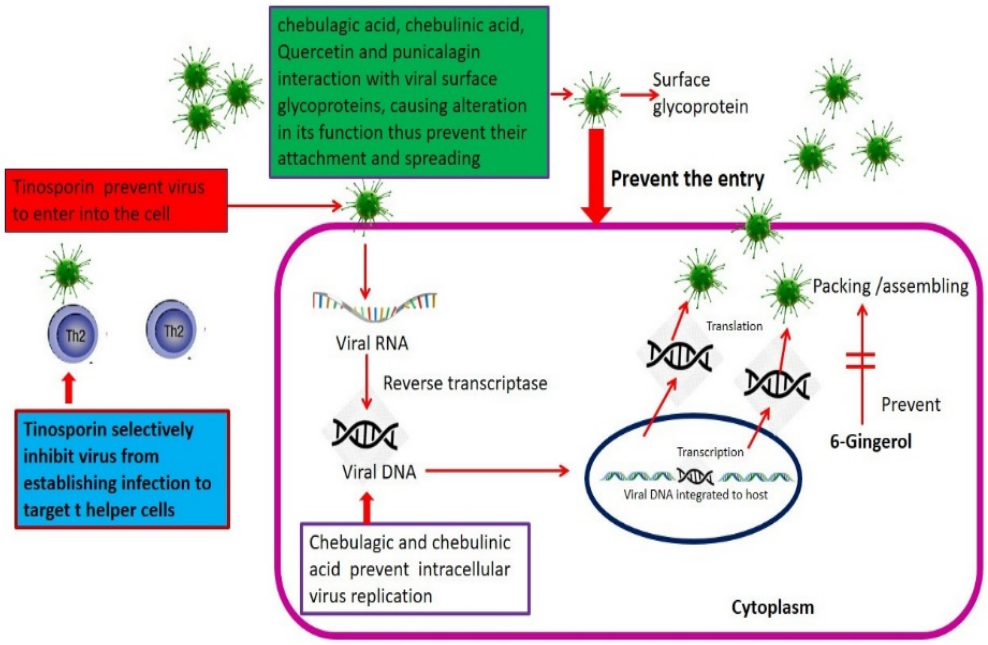

Figure 2: Probable Mechanism of Antiviral Activity of Amrutotharam Kashayam

Antiviral activity (Figure 2)

Flavonoids in *Tinospora cordifolia*[108] possesses antiviral properties. Phosphorylation of protein by cytokines II is inhibited by flavonoids which help in the cell arrest of HIV at integration traction phage of virus. Tinosporin selectively inhibit virus from establishing infection to target t helper cells. The exact mechanism by which it prevents infection of virus and host cell is not known but on analyzing from cell culture incubated with virus doesn't show any series activation of host cell. It suggests either virus is not entering into the cell or, after entry it could not get activated. The antiviral activity of Chebulagic acid, a hydrolysable tannin in *Terminalia chebul*a was exhibited *in-vitro* and *in-vivo* and significant recovery was found due to the inhibition of viral replication in different tissues of chebulagic acid treated mice.

*T. Chebul*a extract, chebulagic acid and chebulinic acid, the hydrolysable tannins exhibit antiviral activity by interacting with viral surface glycoproteins[109]. This prevents the attachment and spread to the VERO cells and in fact prevents cell to cell spread. Chebulagic acid and Punicagilin isolated from the fruits of *T. chebula* blocks the interaction with host cell surface glycosaminoglycans and thus inhibited HSV -1 viral particles, viral binding and penetration to cell as well as secondary infection by targeting the glycoproteins involved in attachment and membrane fusion. Hence the extract of *T. chebula* may target Hepatitis C Viruses, HIV, dengue viruses that uses

glycosaminoglycans as a door for host cell entry. Due to their large molecular weight, chebulagic acid and chebulinic acid is unlikely to penetrate to Vero cells and hence may not interfere in viral replication and hence it binds to viral surface glycoproteins and inhibits cell to cell spread.

6-gingerol of *Zingiber officinale* (Shunthi**)** shows highest binding affinity and interaction with multiple targets of COVID-19 including Viral proteases, RNA binding protein, Spike protein[110].

Quercetin can target influenza viral particles instead of the host cell. Generally, Hemagglutinin (HA) is an essential major glycoprotein on the surface of the influenza virus responsible for entry and fusion of virions. Quercetin could interact with HA and subsequently interfere with virus entry. Quercetin may have a medium binding affinity to influenza HA protein. Quercetin may affect the bound molecules' dynamics and thus alter the binding event. Quercetin efficiently inhibits entry of the influenza A virus, which may be mainly ascribed to its interaction with the HA2 subunit, which mediates the low pH-induced fusion of the viral envelope with the endosomal membrane. Quercetin may target viral surface HA protein and thus inhibit virus infection. Therefore, it can be inferred that quercetin may exert its antiviral activity via interaction with viral HA protein and then inhibit virus entry into the cell[95].

Immunomodulatory Action

Tinosporin is an immunomodulatory agent. It increases the white cell count in pathological states to increase the phagocytes of the foreign material. This leads to the destruction of microbes in infections. *T. cordifolia* and its constituent *α*-D-glucan stimulate NK cells, B cells, and T cells with simultaneous production of various immune-stimulatory cytokines [1] [2] i.e., A novel (1,4)-α-D-glucan from *T. cordifolia* activates the immune system by activating macrophages via TLR6 signaling and NF-κB activation mechanism, leading to cytokine and chemokine production. Melatonin plays an important role as an immunomodulator, as well as performing other physiological functions. It has been reported to be an integral part of the immune system and exerts direct and/or indirect stimulatory effect on both cellular and humoral immunity[111].

One study[109] showed that treatment with *T. chebula* caused the expression of a thick band of protein, indicating increased production of melatonin. Hence, *T. chebula* extract exhibits immune-stimulant action by enhancing melatonin secretion in the pineal gland by exerting direct and/or indirect stimulatory effect on both cellular and humoral immunity; and proliferation of lymphocytes as indicated by the increase in the number of β and T cells which release cytokines and growth factors that regulate other immune cells and secretion of antibodies in the blood.

In a study, an attempt to identify and analyse the chemical constituents in Amrutotharam Kashayam using modern chromatographic and spectroscopic techniques, revealed the presence of phenolics in abundance. Phenolic acids such as quinic acid, protocatechuic acid, gallic acid, and chebulic acid were identified in the formulation[112]. Even though the Mass spectrum chromatogram of the formulation could not validate the phytochemicals of all the constituents especially Amrita (*T. cordifolia*), similar significant researches in this direction can pave new insights in fingerprinting of the final compound to ensure the genuineness and quality of the final product and can bring about newer dimensions in reverse pharmacological approach and drug discovery.

CONCLUSION

Phytochemical screening of the documented formulations in the present study revealed their synergistic antipyretic, antiviral and immunomodulatory potential which revalidates the robust clinical evidences. The scientific analysis of these formulations in this direction with a reverse pharmacological approach will result in a novel drug discovery which is safe and more effective. More over the rapid identification of the exact chemical constituents responsible for therapeutic activity will contribute significantly in selection of unique remedies for emerging and reemerging viral infections in the present arena. The present article throws light on the possible yet undiscovered plant profile, finger printing and probable mechanism of multi-targeted action of single, poly herbal or herbo-mineral formulations exhibited due to its diverse phytochemicals.

Future directions

A scientific validation of the time-tested clinical evidences of the herbs and formulations documented in classics by a reverse pharmacological approach is the need of the hour**.**

Phytochemical screening followed by *in vitro in vivo* studies to prove safety and efficacy.

Incorporation of advanced modern analytical technologies for drug analysis like bioinformatics and other computational technologies to validate the utility of crude drug leads &their combinations to explore their active constituent, interaction of the drug with human models and elucidate the targeted mechanism of action.

Development of standardized manufacturing principles and analytical techniques to ensure the presence of the active principles of all the raw herbs in the finished product for a better therapeutic outcome.

Repurposing of the formulations in our classics to address diverse disease conditions of varied origins.

Isolation of therapeutically effective crude drug extracts can bring about a newer dimension in the field of medicine.

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