Review Article

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PHARMACOLOGICAL ACTIVITY OF CONSTITUENTS OF TRIBHUVAN KIRTI RASA: A REVIEW

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ABSTRACT

Tribhuvan Kirti Rasa is a herbo-mineral preparation mentioned under Jvara chikitsa (Treatment of Fever) in Yogratnakar. It has the potency to cure thirteen types of Jvara (Fever). It comprises five herbal drugs, i.e., *Aconitum Ferox* Wall ex, *Zingiber officinale* Rosc, *Piper nigrum* Linn, *Piper longum* Linn, the root of *Piper longum* Linn. and two mineral drugs, i.e., Cinnabar, Borax in equal ratio. Bhavana (Levigation) is given by *Ocimum sanctum* Linn, *Zingiber officinale* Linn, and *Datura metel* Linn. Most of the drugs in Tribhuvan Kirti Rasa possess Katu (pungent)- Tikta (bitter) in Rasa (Taste), Ushna (hotness) in Virya, and Guna (Property) is Laghu (lightness), Ruksha (dryness) and Tikshna (sharpness) and having Ama pachak (digestive) and anti-inflammatory properties as proven by various studies. Thus, this review article helps to understand that Tribhuvan Kirti Rasa can also effectively pacify Jvara (Fever).

Keywords: Jvara, Tribhuvan Kirti Rasa, Ama, Antipyretic, Anti-inflammatory.

INTRODUCTION

Jvara (Fever) is the king of all diseases [1, 2]. Moreover, Acharya Charak first establishes the theory of Psychosomatic features for the Jvara [3]. There are several formulations described for Jvara in many Ayurvedic texts. Tribhuvan Kirti Rasa is one of them. It is a herbo-mineral formulation. Herbo-mineral complexes are more stable, having faster therapeutic action and a longer shelf life [4]. Three different types of Tribhuvan Kirti Rasa are mentioned in a popular textbook of Rasa Shastra in Rasayoga Sagar [5]. Among these, the most common one is described in Yogaratnakar. It contains two mineral drugs, Hingula (Cinnabar) and Tankana (Borax), and five herbal drugs, Vatsnabha (*Aconitum ferox* Wall ex), Shunthi (*Zingiber officinale* Rosc.), Maricha (*Piper nigrum* Linn.), Pippali (*Piper longum* Linn.), Pippali mool (Root of *Piper longum* Linn.) in equal proportion and Bhavana (Levigation) is given by Tulasi (*Ocimum sanctum* Linn), Ardraka (*Zingiber officinale* Rosc.) and Dhatura (*Datura metel* Linn.) [5,6]. Tribhuvan Kirti Rasa balances Vata-Pitta-Kapha simultaneously and is hence beneficial in Sannipatik Jwara. It is also mentioned in Yakrit (Liver) and Pleeha (Spleen) Vikara (Disorder) and for improving digestion as well [7].

Type of Tribhuvan Kirti Rasa in Rasa Shastra Classics: In Rasayog Sagar, three formulations are mentioned in the name of Tribhuvan Kirti Rasa, and all are indicated in different diseases [5]. The first Tribhuvan Kirti Rasa is Kharaleeya Rasayana (Mortar and Pestle preparation), while the other two are made by the Puta (a measure of heat) method. The first formulation is used in Jvara (Fever), the second one in Prameha (Urinary disease), Kshaya (Tuberculosis), Jvara (Fever), etc., and the third one is used in Udara Roga (GIT Disorders). Acharya has mentioned it as Udaraghna Rasa [8]. The most common one is Kharaleeya Rasayana (Mortar and Pestle preparation). Two formulations contain Vatsnabha (*Aconitum Ferox* Wall ex), Shunthi (*Zingiber officinale* Rosc.), Maricha (*Piper nigrum* Linn.), Pippali (*Piper longum* Linn.), and Tankan (Borax) as common constituents. The third one contains Tamra Patra (Copper), Gandhak (Sulphur), Sanchal (Black salt), Parad (Mercury), and juice of Sambhalu (*Vitex negundo* Linn.) [5].

Etiopathogenesis of Jvara (Fever) in Ayurveda: In Jvara (Fever), vitiated Doshas (functional regulatory factors of the body) enter Aamashaya (stomach) and mixed with Pitta, accompanying the initial Dhatu (Major structural components of the body) "Rasa", blocking the channels carrying Rasa and Sweda (sweat) and affecting the Pachakagni (digestive fire). Ushnata (hotness) of Pachakagni (digestive fire) radiates all over the body and produces Fever [9].

Etiopathogenesis of Fever in Modern Medical Science: Fever is defined as the elevation of core body temperature that exceeds the normal daily variation and occurs in conjunction with an increase in the hypothalamic set point, e.g., from 37-39 °C (98.6-102.2 °F) [10].

In fever, exogenous pyrogens initiate host cells (primarily macrophages) to produce and release endogenous pyrogens such as interleukin 1. These pyrogens are transmitted to the hypothalamic thermoregulatory centre, where they induce the synthesis of prostaglandins, of which PGE2 is the most important. These raise the thermostatic set point to initiate the febrile response [11]. Pain is also an important clinical feature of fever. As per the International Association for the study of Pain (ISAP), pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage [12]. When intense, repeated, or prolonged stimuli are applied to damaged or inflamed tissues, the inflammatory mediators are released, such as bradykinin, nerve-growth factor, some prostaglandins, and leukotrienes contribute to this process. Prostaglandins increase the sensitivity of the terminal to bradykinin and other pain-producing substances [13]. Inflammation is a fundamental pathological change associated with fever and pain. Inflammation is a normal response of mammalian tissue in the body against invading microorganisms. However, during this response, blood cells and plasmic fluid accumulate in the body, which leads to oedema [14]. Chemical mediators like prostaglandins, leukotrienes, nitric oxide, histamine, serotonin, and cytokines are triggered by allergic or chemical irritation, and injury leads to inflammation [15].

DRUG REVIEW

Table 1: Rasa Panchaka (Ayurvedic Pharmacology) of contents of Tribhuvan Kirti Rasa

Drugs	Rasa	Guna	Virya	Vipaka	Doshaghnata	Karma
Cinnabar (HgS) [16]	Tikta, Katu, Kashaya	Ushna	Ushna	-	Vatakaphahara	Jwaraghna, Deepan
Aconitum ferox Wall ex [17]	Madhura	Laghu, Ruksha, Tikshna	Ushna	Katu	Vatakaphahara	Jwaraghna, Swedjanana, Vednasthapan
Zingiber officinale Rosc. [17]	Katu	Guru, Ruksha, Tikshna	Ushna	Madhur	Vatakaphahara	Jwaraghna, Deepan, Pachan, Vednasthapan
Piper nigrum Linn. [17]	Katu	Laghu, Tikshna, Ruksha	Ushna	Katu	Kaphavatahara	Jwaraghna, Swedjanana, Deepan, Pachan
Piper longum Linn. [17]	Katu	Laghu, Tikshna	Anushna	Madhur	Kaphavatahara	Jwaraghna, Deepan, Shoolprashamana
Sodium Tetraborate [7]	Katu	Ruksha, Tikshna	Ushna	-	Vatakaphahara	Deepan
Piper longum Linn. [17]	Katu	Laghu, Ruksha	Ushna	Katu	Kaphavatahara	Jwaraghna, Deepan, Shoolprashamana
Ocimum sanctum Linn. [17]	Katu, Tikta	Laghu, Ruksha	Ushna	Katu	Kaphavatahara	Jwaraghna, Deepan, Pachan, Vednahara
Zingiber officinale Rosc. [17]	Katu	Guru, Ruksha, Tikshna	Ushna	Madhur	Vatakaphahara	Jwaraghna, Deepan, Pachan, Vednasthapan
Datura metel Linn. [17]	Tikta, Katu	Laghu, Ruksha	Ushna	Katu	Kaphavatahara	Vednasthapan

Table 2: Chemical constitution and Pharmacological actions of Tribhuvan Kirti Rasa

Drugs	Chemical constituent	Pharmacological Actions
Aconitum ferox Wall ex[18]	Aconitine, Pseudaconitine, Indaconitine	Analgesic, Diaphoretic
Zingiber officinale Rosc.[19]	Shogaol, Gingerol	Anti-pyretic, Aphrodisiac, Anti-inflammatory, Analgesic, inhibition of prostaglandin release
Piper nigrum Linn. [19]	Piperine, N-isobutyl-11-(3,4- methylenedioxyphenyl)- 2 E	Analgesic, Anti-pyretic, Anti-inflammatory
Piper longum Linn. [20]	Piperine	Anti-inflammatory
Piper longum Linn. [20]	Piperine, methyl-3,4,5- trimethoxycinnamate	Anti-inflammatory
Ocimum sanctum Linn. [21]	Limonine, Luteolin, Linoleic acids	Antipyretic, Anti-inflammatory
Datura metel Linn. [21]	Hyoscyamine, Hyoscine, Tropine	Analgesic, Anticholinergic

Most of the constituents of Tribhuvan Kirti Rasa possess Katu (pungent), Tikta Rasa (bitter taste), and Ushna Virya (hotness in potency), and so does the digestion of Aam, the main causative factor of Jvara. Also, Laghu (Lightness) and Tikshna Guna (sharpness property) intensify the Agni and cure Agnimandya (depleted digestive fire). Ushna Virya (hotness in potency) increases perspiration and relieves the Sroto-avrodha (obstruction of channels). In this way, it cures Jvara (fever).

In Drug & Cosmetic Act, 1940 *Aconitum ferox* Wall ex and *Aconitum chasmanthum* Staphf. ex is mentioned for Vatsnabha [22]. *Aconitum ferox* Wall ex and *Aconitum chasmanthum* Staphf. ex is the endangered species and rarely found. So, these days *Aconitum balfourii* Staphf is used in place of *Aconitum ferox* Wall ex and *Aconitum chasmanthum* Staphf. ex [23].

Pharmacological properties of constituents of Tribhuvan Kirti Rasa: To hypothesize the mode of action of this polydrug formulation, a general description of the individual drugs, Ayurvedic pharmacology, and experimental research work carried out on the pharmacological action of the individual drug on fever and inflammation is compiled here.

Cinnabar (Hingula): It is the chief ore of mercury due to the higher percentage of mercury present in it [24]. Chemically it is a red sulfide of mercury. It contains about 86% of mercury and 14% of sulphur [25]. Hingula possesses antipyretic properties [26,27]. Deepan (digestion and metabolic enhancing) property [28,29] and Pachan (improving digestion) property [27].

***Aconitum ferox* Wall ex (Fam. Ranunculaceae):** It is a shrub having blue flowers, leaves are like the *Vitex negundo* Linn. plant, the shape of its tuber is like a cow's nipple, and the tuber is not bigger than five fingers in width. It is found in the Himalayan area from Garhwal to Sikkim [30]. Roots of *Aconitum ferox* Wall ex has anti-inflammatory property [31].

***Zingiber officinale* Rosc. (Fam. Zingiberaceae):** It is a perennial herb. The flowers are of greenish yellow color. Primarily cultivated in hot and humid places. Shunthi is the dried rhizome of *Zingiber officinale* Rosc. [32].

Anti-inflammatory activity: Gingerol, shogaol, and other substances in *Zingiber officinale* Rosc. inhibit leukotriene biosynthesis and prostaglandin by suppression of 5-lipoxygenases or prostaglandin synthetase. They also inhibit the production of pro-inflammatory cytokines such as IL-1, IL-8, and TNF-α [33]. Shogaol down-regulates inflammatory iNOS and COX-2 gene expression in macrophages [34]. The hexane fraction of extract of rhizome of *Zingiber Officinale* Rosc. hampered the excessive production of PGE2, NO, TNF-α, and IL-1β [35]. A study done on gingerols can impede the LPS-induced COX-2 expression. Therefore, capable of inhibiting inflammatory mediators like PGE2 [36]. A clinical study on 30 patients showed fine powder of *Zingiber officinale* Rosc. manifested a significant improvement in symptoms of Rheumatoid Arthritis, taken at a dose of 2 gm BD before meal [37]. In another Clinical study, 28 male runners were given capsules of 500 mg of fine powder of *Zingiber officinale* Rosc, which reduced the post-exercise several cytokines that promote inflammation, such as plasma IL-1β, IL-6, and TNF-α [38].

Analgesic activity: The analgesic effect of *Zingiber officinale* Rosc. at a dose of 2 gm in 36 patients to cure muscle pain [39].

***Piper nigrum* Linn. (Fam. Piperaceae):** It is a woody perennial climbing plant having a dimorphic branching pattern. Axillary buds continue branches. Its flower is sessile, bracteate, and uni/bisexual [40].

Anti-pyretic activity: An *in-vivo* study was conducted on piperine to check its antipyretic activity using Baker's yeast-induced pyrexia method. Piperine (20 mg/Kg and 30 mg/Kg) showed a better antipyretic effect than the standard drug Indomethacin [41].

Anti-inflammatory activity: *In-vitro* and *in-vivo* studies were done by taking IL-1β stimulated fibroblast derived from rheumatoid arthritis patients and by carrageenan-induced paw oedema method. Piperine decreased the production of IL6 and MMP13 and reduced the production of PGE2 in a dose-dependent manner [42].

Analgesic activity: An *in-vivo* study reported analgesic activity of Piperine due to blockage of prostaglandins at a dose of 20 mg/Kg and 30 mg/Kg intraperitoneally [43]. A similar study showed significant analgesic activity of piperine [44].

Digestive stimulant activity: A comparative *in-vivo* digestive stimulant activity study was done between *Piper nigrum* Linn. and Trikatu (an equal amount mixture of fine powders of *Zingiber officinale* Rosc, *Piper nigrum* Linn. and *Piper longum* Linn), at a dose of 300 mg/Kg. Both fine powders raised the digestive enzymes, namely alkaline phosphatase, lipase, amylase, and bile juice, and hence proved good digestive activity [45].

***Piper longum* Linn. (Fam.- Piperaceae):** It is an aromatic climber in the hotter parts of India and the central Himalayas. The stem is creeping, jointed, and thickened at the nodes [46].

Piperine is the main active constituent in the *Piper longum* Linn. which has reported antipyretic, analgesic [47] and anti-inflammatory properties [48].

Anti-inflammatory activity: A comparative *in-vivo* anti-inflammatory study of 2 *Piper longum* Linn varieties by the Carrageenan-induced paw oedema method was done at 200 mg/Kg. Piper *longum* Linn. manifested a marked anti-inflammatory effect. Moreover, a small variety of *Piper Longum* Linn. revealed better results than large *Piper longum* Linn. [49]. An *in-vitro* study was done on Piper longum Linn's active principles, Ethyl 3',4',5-trimethoxycinnamate, and piperine, extracted from the hexane and chloroform extracts of Piper longum Linn. Both the extracts inhibited the TNF-α-induced expression of ICAM-1 [50].

Digestive activity: A study carried out on herbs of *Zingiber officinale* Rosc, *Piper nigrum* Linn, and *Piper longum* Linn individually to detect their effect on digestive enzymes substantiated that *Piper longum* Linn. manifested the best increase of digestive enzymes by significantly intensifying the activity of protease, amylase, and lipase, followed by *Piper nigrum* Linn. and *Zingiber officinale* Rosc [51].

Borax (Tankan)

It is also named Sodium tetraborate decahydrate. It is mentioned under Kshar Varga [Alkali]. Borax has 11.03% of boron. It occurs as a natural deposit in the form of tough crystalline masses formed by water evaporation on the shores of dried-up lakes in India, Tibet, and Nepal [52]. Borax has Deepan (digestion and metabolic enhancing) property [53].

Anti-inflammatory activity: An *in-vitro* anti-inflammatory activity of Borax by membrane-stabilizing and protein inhibitory methods. The fine powder of Borax was compared with standard Diclofenac sodium. Fine powder of Borax showed significant membrane stabilizing activity of 72.22% and protein inhibition activity of 94.65% at a concentration of 200 µg/mL[54]. Boron also reduces levels of inflammatory biomarkers [55].

***Piper longum* Linn. (Fam.- Piperaceae):**

Analgesic activity: An *in-vivo* analgesic study was done on the aqueous suspension of fine powder of the root of *Piper longum* Linn. in three different doses (200, 400, and 800 mg/kg). The analgesic effect of the 400 and 800 mg/kg doses of *Piper longum* Linn. was like NSAID's effect, indicating that the plant root possesses a potent NSAID-type of analgesia [56].

***Ocimum sanctum* Linn. (Fam. Labiate)**

It is an erect, many-branched, and aromatic herb approx. 75 cm in height. It is found throughout India and is considered a sacred plant [57].

Anti-pyretic activity: An *in-vivo* antipyretic study of Ethyl acetate extract of *Ocimum sanctum* Linn. roots through Brewer's yeast model, in different doses of 30 mg/Kg, 100 mg/Kg, and 300 mg/Kg revealed the reduction in temperature. Among which 300 mg/Kg dose showed the best result [58]. The antipyretic activity of *Ocimum sanctum* Linn. fixed oil was conducted by testing it against typhoid-paratyphoid A/B vaccine-induced pyrexia model in rats. Oil significantly reduced the febrile response due to its

prostaglandin inhibitory activity [59]. A decoction prepared from the roots of *Ocimum sanctum* Linn. plant is used as a diaphoretic in malarial fever [60].

Anti-inflammatory activity: An *in-vivo* study by various media, namely Chloroform, n-Hexane, Butanol, Ethyl acetate, and water extracts of *Ocimum sanctum* Linn. was performed. The Ethyl acetate extract showed the most remarkable anti-inflammatory effect [58]. Another *in-vivo* study was carried out through *Ocimum sanctum* Linn. Patra Kalka (leave's paste). The anti-inflammatory response of the paste was 88.15% as that of the effect observed by the standard drug [61]. An *in-vivo* study evaluated the acute and chronic anti-inflammatory effects of methanolic extract (500 mg\Kg) and aqueous extract of *Ocimum sanctum* Linn. by Carrageenan induced pedal oedema method by suppressing PGE2, leukotriene, and arachidonic acid [62]. Another study evaluated Linoleic acid in *Ocimum sanctum* Linn. oil's significant anti-inflammatory activity against PGE2, leukotriene, and arachidonic acid [63].

Analgesic activity: The analgesic effect of Ethyl acetate extract of *Ocimum sanctum* Linn. root was done through various models. The extract showed better analgesic activity in the acetic acid-induced writhing model than a hot plate and tail immersion method [58]. In another *in-vivo* study carried out by the *Ocimum sanctum* Linn. oil, it was found to be effective against acetic acid-induced writhing method but lacking analgesic effect in other experimental methods like tail flick, tail clip, and tail immersion methods [64].

***Datura metel* Linn**. (**Fam.- Solanaceae):** It is a perennial shrub having alternate leaves, dark green, ovate, and shallowly lobed. Flowers are of various colours, ranging from white to yellow and light to dark purple, large, and trumpet-shaped with a sweet fragrance. The fruit is like a table tennis ball covered with short spines [65].

Anti-inflammatory activity: An *in-vitro* study to evaluate the anti-inflammatory effect of *Datura metel* Linn leaves showed a significant result [66].

DISCUSSION

Tribhuvan Kirti Rasa is a paramount Ayurvedic drug for treating thirteen types of fever. Mainly it is prescribed for Sannipatik Jvara. Two conditions have been mentioned in the pathogenesis of Jvara: Agnimandya (depleted digestive fire), which leads to Ama formation, and Srotoavrodha (obstructive pathology occurring in channels), by that Ama. As most of the contents of Tribhuvan Kirti Rasa have Katu (Pungent), Tikta Rasa (bitter taste), Laghu (Lightness), Ruksha Guna (dryness property), and Ushna Virya (hotness), so it intensifies the Agni and consequently causes digestion of Ama. Also, its content *Zingiber officinale* Rosc. is the principal drug for Ama Pachan (enhancing digestion). Furthermore, in Tribhuvan Kirti Rasa, Bhavana (Levigation) is given by three different Swarasa (juice). 1st by *Ocimum sanctum* Linn. Swarasa, 2nd by *Zingiber officinale* Rosc. Swarasa (juice) and in the end by *Datura metel* Linn. Swarasa. All these Bhavana Dravya have VataKaphahara property, and Ushna Virya (hotness) so help in Agni Deepan (digestion and metabolic enhancing) and hence do Pachan (improving digestion) of Ama.

Ushna and Tikshna Guna, along with Vyavayi (substances with quick spread even without digestion), Vikasi (property of substances resulting in the rapid spread and action), and Ashu Guna (quick property) of *Datura metel* Linn. penetrate the blockage of Swedavaha Srotas (sweat channel) owing to Ashu Guna (quick property) peripheral vessels are dilated, and heat loss takes place which ultimately decreases the temperature. Also, Vyavayi (substances with rapid spread even without digestion) and Vikasi Guna (property of substances resulting in quick spread and action) of *Aconitum ferox* Wall ex and *Datura metel* Linn. enhance the bioavailability of the drug. *Aconitum ferox* Wall ex increases secretion of Sweat and alleviates the obstruction of Swedvaha Srotas (sweat channel). Its alkaloid aconite further depresses the activity of all nerve terminals; therefore, it tends to relieve pain which is generally a secondary symptom associated with fever. It also acts as a Rasayana (rejuvenation), providing immunity against various pathogens. Cinnabar is Yogvahi (carrier of properties), so it elevates the efficacy of other contents. Borax possesses anti-inflammatory and digestive properties. It has Ushna Virya (hotness) and therefore digests Ama, reducing body pain associated with Jvara.

Moreover, it is an excellent antidote to aconite. As *Aconitum ferox* Wall ex is used in Tribhuvan Kirti Rasa, Borax can neutralize its toxicity effect if by chance occurs. *Zingiber officinale* Rosc, *Piper nigrum* Linn, and *Piper longum* Linn have Ushna Virya (hotness) along with Katu Rasa (pungent taste), which is required for digestion of Ama, the causative factor of Jvara (fever). *Piper nigrum* Linn. has Pramathi property (stirring or agitating action), so it clears the obstruction of Srotas (channels). Roots of *Ocimum sanctum* Linn. are known for diaphoretic action.

Modern Science believes that various inflammatory mediators are released preceding fever. These inflammatory mediators release pyrogenic cytokines like IL-1, IL-6, TNF, and IFN. These cytokines reach into the hypothalamus temperature regulatory centre through blood and release prostaglandins, ultimately elevating temperature and producing fever.

So, through this pathogenesis, we can conclude that the drugs which possess an anti-inflammatory effect would also have an antipyretic effect. Here in Tribhuvan Kirti Rasa, most of the contents, namely *Aconitum ferox* Wall. ex, *Piper nigrum* Linn, *Zingiber officinale* Rosc, *Piper longum* Linn, Borax, *Ocimum sanctum* Linn. and *Datura metel* Linn. have anti-inflammatory activity, so they also act as antipyretic.

CONCLUSION

According to Ayurvedic Pharmacology, most of the contents of Tribhuvan Kirti Rasa have Ushna Virya (hotness), so cure Agnimandya (depleted digestive fire) and thereby help in Pachan (enhancing digestion) of Ama, which is the main causative factor of Jvara. Also, as mentioned in earlier possible experimental work, it has been proven that the phytochemicals of its constituents possess therapeutic actions such as antipyretic, anti-inflammatory, and analgesic. Thus, all its ingredients and the whole formulation contribute to antipyretic and anti-inflammatory activity. So Tribhuvan Kirti Rasa can also be considered a potent formulation for further studies to validate its antipyretic effect.

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