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ORA - Experimental Study

Development and primary bioinformatics analysis of '*Mishi Paanak*' – An Ayurveda-inspired cooling drink

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ABSTRACT:

Background: Seasonal variations significantly impact human physiology, with *Grishma Ritu* (summer) specifically associated with excessive heat and dehydration, particularly in hot geoclimatic regions like India. This leads to an increase in *Pitta dosha* and a heightened risk of heat-related health issues. Ayurveda emphasizes the consumption of sweet, cold, liquid, and unctuous foods to maintain physiological balance and prevent dehydration during intense summers. Inspired by these traditional principles, *Mishi Paanak* is developed as a novel, Ayurveda-inspired natural summer coolant to provide hydration, restore energy, and soothe the effects of summer heat. **Materials and Methods**: *Mishi Paanak* recipe is formulated using fennel seeds (Mishi, *Foeniculum vulgare* Mill.), poppy seeds (*Papaver somniferum*), watermelon juice (*Citrullus lanatus* (Thunb.) Matsum. & Nakai), and *Khanda Sharkara* (rock candy), prepared with water. A network pharmacology-based approach was adopted to justify the role of these ingredients and understand their mode of action. **Results**: Phytochemical analysis identified 20 common compounds shared across the three main ingredients, including quercetin, kaempferol, linoleic acid, linolenic acid, nicotinic acid, and thiamine. The study identified 65 common genes between the phytochemical targets and dehydration-related gene sets. Ten top hub genes were isolated through Cytohubba analysis: KDR, ESR2, AKT1, IGF1R, MMP9, PTK2, SRC, MMP2, PPARG, and EGFR1929. These genes collectively target 37 most common pathways responsible for dehydration. Mechanistic insights reveal that key phytochemicals like quercetin and kaempferol modulate anti-inflammatory pathways (AKT1, MMP9), linoleic and linolenic acids influence epidermal hydration (PPARG, EGFR), and citrulline enhances vasodilation via nitric oxide. **Conclusion**: *Mishi Paanak* is presented as an effective natural Ayurveda-inspired summer coolant designed to combat the effects of excessive heat and dehydration during *Grishma Ritu*. The beverage offers easy preparation, cost-effectiveness, and aligns with Ayurvedic principles, making it a healthy alternative to aerated and processed beverages. The network pharmacology analysis scientifically validates that this combination of herbs and the drink prepared positively impacts dehydration pathways, demonstrating novel design and synergistic effects at the molecular level.

KEYWORDS: Ayurveda health drink, Ayurveda recipe, coolant, *Mishi Paanak*

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1. INTRODUCTION:

Seasonal variations have a lasting impact on the physiology of the human beings. For instance, *Grishma Ritu* (summer season), the sun's intense rays dry up the environment, leading to increased heat and dehydration especially in countries like India with hot geoclimatic conditions. During this time, Ayurveda emphasizes the consumption of sweet, cold, liquid, and unctuous foods and drinks to maintain balance and health. [1] Ayurveda suggests that individuals consuming such cooling and nourishing diets like cold and sweet *Paanak* or *Mantha* (a type of liquid preparation), can avoid weakness and combat the intense summer heat. [2]

Inspired by these principles, *Mishi Paanak* has been developed as an innovation to address the challenges of summer. This is a novel recipe developed with a view to decipher cooling effect of combination of different herbs. While not mentioned in classical Ayurvedic texts, this beverage combines fennel seeds (*Foeniculum vulgare* Mill.) known as *Mishi* in Ayurveda which are traditionally used as a part of coolant drinks in some Indian states like Rajasthan, poppy seeds (*Papaver somniferum*) known as *Khus Khus Beeja*, Watermelon Juice (*Citrullus lanatus* (Thunb.) Matsum. & Nakai) or *Kalinda Phala*, and natural sweeteners such as *Khanda Sharkara* (rock candy) or *Guda* i.e. jaggery along with normal water to create a refreshing, hydrating, and nourishing drink. This study is a novel approach developed with an aim to explore the Ayurveda principles behind the use of these ingredients for different health benefits combining with evidence based on network pharmacology. *Mishi Paanak* serves as a perfect coolant, replenishing lost energy, soothing aggravated *Pitta Dosha*, and preventing dehydration, making it an ideal choice for the summer season. This is easy to prepare, cost effective and can be used as a healthy alternative to aerated and processed drinks available in market. The network pharmacology approach was also adopted to understand the mode of action and mechanism of this coolant in conditions like dehydration. The action of phytochemicals in the contents of *Mishi Paanak* was assessed on the target genes responsible for the dehydration. The main objective was to analyse whether there are any common gene pathways between the phytochemicals of the contents of the *Mishi Paanak* and condition of dehydration especially summer related heat disorders.

2. MATERIALS AND METHODS

Present study is an original research article involving the steps for development and preparation of Ayurveda coolant drink. The network pharmacology-based approach (molecular docking-based approach) is adopted to justify the role of ingredients used in the preparation of the Ayurveda coolant drink i.e. *Mishi Paanak*. Network pharmacology based approach is detailed in the results section mentioned below.

Procurement of Raw botanicals or contents

All the required raw botanicals were obtained from the local market in New Delhi. The composition of the test preparation is outlined in Table 1. The authentication of raw drugs was done at RRDR lab of All India Institute of Ayurveda, New Delhi.

Table No. 1: Ingredients, Latin name, parts used and quantity of the components included in *Mishi Paanak*

Sr. No.	Ingredient	Latin name	Part used	Quantity	Authentication ID
1.	*Mishi* (Fennel seeds)	*Foeniculum vulgare* Mill.	Dry seeds	50 gm	RRDR/AIIA/70
2.	*Khus Khus* (Poppy seeds)	*Papaver somniferum* L.	Seeds	25 gm	RRDR/AIIA/72
3.	*Kalinda Rasa* or Watermelon Juice	*Citrullus lanatus* (Thunb.) Matsum. & Nakai	Extracted juice from the fresh fruit	100 ml	RRDR/AIIA/71
4.	*Mishri* (Rock candy or sugar)	----------	Granular Form	50 gm	----------

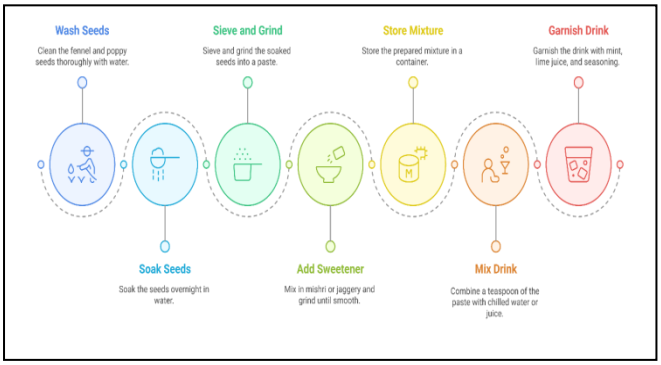

Figure No. 1 – Steps in preparation of *Mishi Paanak* recipe

Steps in recipe preparation

1. Wash the fennel seeds and poppy seeds thoroughly with clean water.
2. Soak 1 cup of fennel seeds and 1/2 cup of poppy seeds overnight in 2 cups of water
3. The next morning, sieve the mixture and grind the soaked seeds into a fine paste with the help of mixer grinder or food processor, utilizing the soaked water to retain its nutrients and flavour.
4. Add 1/2 cup of Mishri i.e. sugar or jaggery to the paste and grind again until smooth.
5. Store the prepared mixture in a container for future use.6. While serving mix 1 teaspoon of the paste with 100ml watermelon juice. Chilled water may be added as per one's desire.
6. Garnish the drink with fresh mint leaves, a squeeze of lime juice, and a pinch of salt and pepper. Steps of the recipe preparation are illustrated in figure No. 1 given below-

Results for Network pharmacology of contents of *Mishi Paanak* drink in condition of dehydration.

1) The phytochemicals for the contents of the *Mishi Paanak* drink namely *Shatapushpa* (*Foeniculum vulgare* Mill), *Kalinda* (*Citrullus lanatus* (Thunb.) Matsum. & Nakai) and *Khus Khus* (*Papaver somniferum* L) were compiled from the online database IMPATT 2.0 (Indian Medicinal Plants, Phytochemistry and Therapeutics 2.0, Available from: https://cb.imsc.res.in/imppat/home). Phytochemicals in seeds and whole plant of *Shatapushpa* and *Khus Khus* seeds were compiled while those in fruit and whole plant for watermelon were selected. The results were stored in Microsoft excel sheet format.

2) The SMILES (Simplified Molecular Input Line Entry System) and PubChem ID for each of the Phytochemicals were derived through the IMPATT database and PuBChem (https://pubchem.ncbi.nlm.nih.gov/) respectively. Total phytochemicals for *Shatapushpa* seeds were 101, for watermelon were 103 while for Poppy seeds were 83.

3) The common Phytochemicals amongst the three ingredients were sorted using the Venn diagram

(Available from: https://bioinfogp.cnb.csic.es/tools/venny/). Common phytochemicals in all the three contents were nine in number, common for both *Shatapushpa* and watermelon were 6 while 3 each were common for *Shatapushpa* and Poopy seeds along with watermelon and poppy seeds as well. These results are presented in form of venn diagram in Figure no. 2 while Table No. 2 details the common constituents. The Phytochemical name, SMILES entry as well as PubChem ID of the common phytochemicals are presented in the Table No. 3.

Amongst the total 397 phytochemicals obtained from IMPPAT, 103 compounds (26%) passed LIPINSKI rule and found to have drug likeliness score >0.4 in MOLSOFT. Amongst these compounds, 20 are common in all the three components of *Mishi Panak* which were further considered for the network analysis.

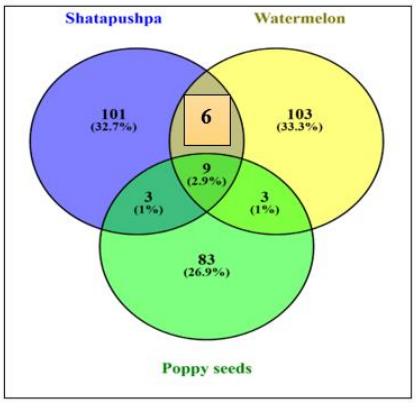

Figure No. 2- Common phytochemicals identified amongst the contents of *Mishi Paanak*

Table No. 2: Common phytochemicals in the contents of *Mishi Paanak*

9 common elements in "*Shatapushpa*", "Watermelon" and "Poppy seeds	**6 common elements in "*Shatapushpa*" and "Watermelon"**	**3 common elements in "*Shatapushpa*" and "Poppy seeds"**	**3 common elements in "Watermelon" and "Poppy seeds"**
Stearic acid	Myristic acid	Kaempferol	2-Pentylfuran
Stigmasterol	Octanal	Quercetin	Folic
beta-Sitosterol	Erythritol	Linolenic acid	1-Hexanol
Thiamine	Limonene		
Riboflavin	Decanal		
Nicotinic acid	Nonanal		
Palmitic acid			
Oleic acid			
Linoleic acid			

Table No. 3: SMILES, Phytochemical identifier and PubChem ID of the phytochemicals

Phytochemicals	**SMILES**	**Phytochemical identifier**	**PUBCHEM ID**	**Passed through ADME evaluation and MOLSOFT drug likeliness study**
Stearic acid	CCCCCCCCCCCCCCCCCC(=O)O	IMPHY004631	5281	Yes
Stigmasterol	CC[C@@H](C(C)C)/C=C/[C@H]([C@H]1CC[C@@H]2[C@]1(C)CC[C@H]1[C@H]2CC=C2[C	IMPHY014842	5280794	Yes

	@]1(C)CC[C@@H](C2)O)C			
beta-Sitosterol	CC[C@@H](C(C)C)CC[C@H]([C@H]1CC[C@@H]2[C@]1(C)CC[C@H]1[C@H]2CC=C2[C@]1(C)CC[C@@H](C2)O)C	IMPHY014836	222284	Yes
Thiamine	OCCc1sc[n+](c1C)Cc1cnc(nc1N)C	IMPHY000005	1130	Yes
Riboflavin	OC[C@H]([C@H]([C@H](Cn1c2c(nc3c1cc(C)c(c3)C)c(=O)[nH]c(=O)n2)O)O)O	IMPHY000846	493570	Yes
Nicotinic acid	OC(=O)c1cccnc1	IMPHY007357	938	Yes
Palmitic acid	CCCCCCCCCCCCCCCC(=O)O	IMPHY007327	985	Yes
Oleic acid	CCCCCCCC/C=CCCCCCCCC(=O)O	IMPHY011797	965	Yes
Linoleic acid	CCCCC/C=CC/C=CCCCCCCCC(=O)O	IMPHY014990	3931	Yes
Myristic acid	CCCCCCCCCCCCCC(=O)O	IMPHY000060	11005	Yes
Octanal	CCCCCCCC=O	IMPHY000795	454	Yes
Limonene	CC1=CCC(CC1)C(=C)C	IMPHY014988	22311	Yes
Decanal	CCCCCCCCCC=O	IMPHY006970	8175	Yes
Nonanal	CCCCCCCCC=O	IMPHY003525	31289	Yes
Kaempferol	Oc1ccc(cc1)c1oc2cc(O)cc(c2c(=O)c1O)O	IMPHY004388	5280863	Yes
Quercetin	Oc1cc(O)c2c(c1)oc(c(c2=O)O)c1ccc(c(c1)O)O	IMPHY004619	5280343	Yes
Linolenic acid	CC/C=CC/C=CC/C=CCCCCCCCC(=O)O	IMPHY012723	860	Yes
2-Pentylfuran	CCCCCc1ccco1	IMPHY005811	19602	Yes
Folic	OC(=O)CC[C@@H](C(=O)O)NC(=O)c1ccc(cc1)NCc1cnc2c(n1)c(=O)nc([nH]2)N	IMPHY006310	135398658	Yes
1-Hexanol	CCCCCCO	IMPHY007171	142645	Yes

4) The ADME related information drug absorption and pharmacokinetic data for each of the phytoconstituent was compiled and analysed using the free online available SWISS ADME software (http://www.swissadme.ch/).

5) All the phytochemicals were screened for the bio-availability, ability to cross blood brain barrier (BBB), at 2 out of 5 criteria (Lipinski, Ghose, Veber, Egan, and Muegge) to evaluate drug the likeness in order to determine if a chemical compound has properties that would likely make it an orally active drug in humans.

6) Further the gene targets for each of the phytochemicals were screened using the freely available SWISS Target Prediction software (http://swisstargetprediction.ch/)

7) The gene targets for each of the phytochemicals having the probability above 0.5 were compiled and separated. A probability threshold of 0.5 was selected to ensure a balance between sensitivity and specificity in target identification. This threshold implies that the predicted interaction has at least a 50% likelihood of being true, thereby reducing the inclusion of low-confidence or spurious predictions

while retaining a sufficient number of candidate targets for downstream network analysis. The rationale for using a threshold of 0.5 is supported by prior literature where similar cutoffs have been employed to maintain reliability in computational predictions. Moreover, inclusion of targets above this threshold enhances the biological relevance and interpretability of the constructed compound–target–pathway network, allowing for more accurate elucidation of the potential pharmacological mechanisms of the phytochemicals under investigation. The targets were collated and deduplicated resulting in list of 104 common gene targets for the 20 common phytochemicals.

8) The 3504 Gene targets for the Dehydration condition were copied from the free online software named GENECARD (https://www.genecards.org/Search/Keyword?queryString=Dehydration). 65 common genes from the phytochemical targets and dehydration were identified. Figure No.3 depicts the common gene targets between dehydrations and contents of *Mishi Paanak.*

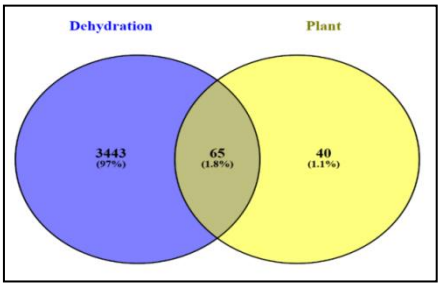

Figure no 3 Common gene targets between dehydration and contents of *Mishi Paanak*

9) Protein- Protein interaction was identified for 65 genes and 10 top hub genes were isolated using the online available networking software, 'Cytohubba' from "Cytoscape" freely online available from https://cytoscape.org/. The cytoscape analysis is presented in the figure No.4 as shown below

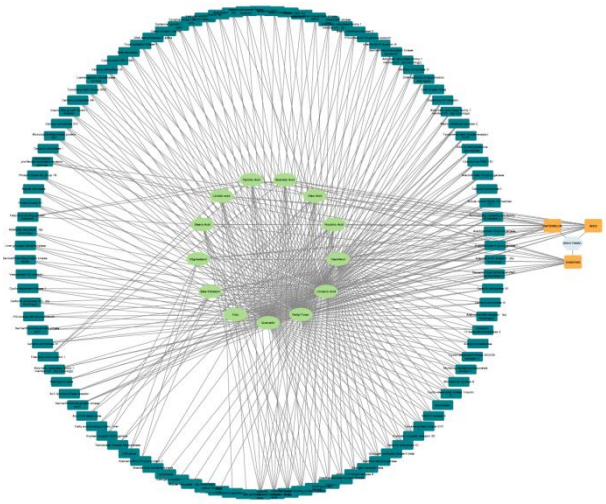

Figure No. 4: Cytoscape analysis for *Mishi Paanak* recipe

10) The top ten genes were KDR, ESR2, AKT1, IGF1R, MMP9, PTK2, SRC, MMP2, PPARG and EGFR. The gene network diagram for the *Mishi Paanak* top genes is presented in the figure No. 5 as given below. Common pathways for the herbs with the condition dehydration were then identified.

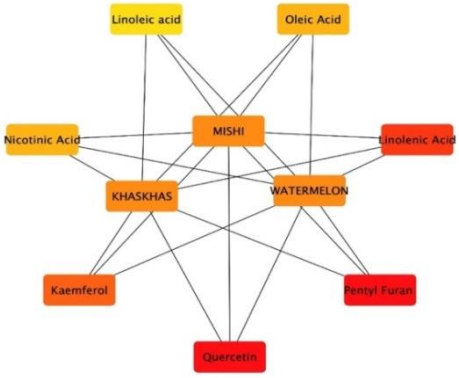

Figure No. 5 – Cytohubba analysis for top 10 genes

Figure No. 6: Results of Gene enrichment Analysis

11) Gene enrichment analysis result presented from g:Profiler, a freely available online from (https://biit.cs.ut.ee/gprofiler/gost) showing pathways associated with Mishi Panak. The results indicate functional categories such as molecular functions (MF), biological processes (BP), cellular components (CC), and pathway enrichment (KEGG, Reactome, etc.). The Gene enrichment analysis results are presented in the figure No. 6. This figure highlights that the top ten genes of the phytochemicals target the 37 most common pathways responsible for dehydration in the individuals. The common pathways related to the management of dehydration are depicted in figure number 6, along with their Padjj values.

12) Observations of Cytohubba analysis (refer to figure No. 4)- The network was developed to highlight the shared and unique compounds among these botanicals, illustrating the chemical connectivity and potential synergistic interactions. Central Nodes indicate the Botanical Sources including *Mishi* (*Shatapushpa*), *Khus Khus* seeds and watermelon. These are depicted with medium orange-coloured rectangles, signifying the primary materials under study. Peripheral Nodes denote the Phytoconstituents or the peripheral compounds are color-coded based on their degree of connectivity and potential biological significance. Yellow shades represent highly common fatty acids such as linoleic acid, oleic acid and nicotinic acid, orange shades represent flavonoids and important bioactive Kaempferol while red shades represent critical bio actives associated with potent antioxidant and anti-inflammatory effects like Linolenic acid, Pentyl Furan and Quercetin. The edges (black lines) depict direct associations between a botanical source and a constituent, either based on experimental identification or from literature-supported data. Multiple connections from a single botanical source to different compounds suggest chemical richness and poly pharmacological potential. The adjusted p values and related details of the phytochemical analysis are presented in excel sheets attached as supplementary data with this file. The heatmap or cluster diagram showing which phytochemicals hit which genes is shown in the excel sheet as well.

3. DISCUSSION

Ayurveda promotes prevention of disease alongside the therapeutic intervention while focusing on the important non pharmacological and lifestyle related intervention like diet as well. The different drinks in form of *Paanak* can help in promotion of health along with combating the summer heat and conditions like dehydration. This article throws light upon the methodology for the preparation of recipes based on Ayurveda principles and in silico-based understanding of pharmacological characteristics. The network pharmacology for the common phytochemicals involving the contents of *Mishi Paanak* was performed

as this is a novel recipe and not directly mentioned in the Ayurveda texts. This beverage combines fennel seeds (*Mishi* or *Shatapushpa*, *Foeniculum vulgare* Mill.), poppy seeds (*Khus Khus Beeja, Papaver somniferum*), watermelon juice (*Kalinda Phala*, *Citrullus lanatus* (Thunb.) Matsum. & Nakai), and natural sweeteners like *Khanda Sharkara* (rock candy) or *Guda* (jaggery), prepared with water.

Mishi Paanak drink can be prepared at home and contains different health promoting and traditional herbs like *Shatapushpa* seeds and watermelon. This preparation can be stored in refrigerator for 3-4 days. Cooling effect of the drink is enhanced when served chilled however the addition of fresh watermelon at room temperature itself can provide the desired freshness. The drink tastes better when served cool and should be stored in refrigerator preferably at 4 degrees Celsius.

Properties of *Shatapushpa* i.e. Fennel seeds

Fennel seeds or *Saunf*, *Mishi* or *Mishreya* botanically known as *Foeniculum vulgare* Linn. is a versatile and ancient Indian spice that stands out for its unique properties. Unlike most spices, which are generally hot and can be harsh on the stomach, fennel seed is known for its sweetness with a slightly bitter and pungent taste. It is light to digest (*Laghu*) and dry (*Rooksha*) in nature, offering a combination of sweet (*Madhura*), pungent (*Katu*), and bitter (*Tikta*) in taste, with a sweet aftertaste (*Madhura Vipaka*) once digested. [3] Its potency is described as hot (*Ushna*), but it can also be considered cooling according to certain texts like *Dhanvantari Nighantu*. [4]

Due to above mentioned properties fennel seed can be highly effective in balancing *Vata* and *Kapha Dosha* and aid in treating chronic respiratory conditions that lead to emaciation, such as tuberculosis. *Sharangdhara* has highlighted its *Deepana* properties making it an excellent herb for digestion related complaints. [5] Thus fennel seed aid in improving digestion (*Agnikrut*) acting as a heart tonic (*Hridya*), promoting cardiovascular health. It is useful for addressing various digestive and respiratory issues, such as relieving pain in the female reproductive system (*Yonishoolanut*), treating worm infestations (*Krumi*), constipation (*Baddhavitghna*), and disorders related to *Vata Dosha*. It iseffective in managing conditions like burning sensations (*Daha*), anorexia (*Aruchi*), vomiting (*Chardi*), and respiratory issues like cough (*Kasa*). [6] *Shatapushpa* has multisystemic activities enhancing the function of digestive, endocrine, reproductive and respiratory system. [7] These have been extensively studied for their digestive properties as they decrease the appetite without reducing the food consumption. [8] It also possesses anti-inflammatory and hyperlipidaemic, anti-oxidant [9] properties thus helpful in management of metabolic syndrome. [10] Fennel seed powder has been traditionally used as a galactagogue and source of oestradiol also helpful in management of post-menopausal syndrome. [11] Thus, this drink can be prescribed in elderly women suffering from symptoms like hot flushes and for promoting the hormonal balance in women suffering from PCOD/PCOS like conditions. [12]

Properties of *Khus Khus* or Poppy Seed

Poppy seeds known as *Khus Beeja* or *Khas Khus Tila* are known for their ability to enhance beauty, induce natural sleep, improve digestion amongst other health benefits. They are also used to garnish other food items. Poppy seeds are known for their aphrodisiac

properties (*Vrushya*) and their ability to improve strength and immunity (*Balya*). [13] These seeds are heavy (*Guru*) and useful in treating gastritis and other digestive issues. They increase *Kapha dosha* and decrease *Vata dosha*, making them beneficial for conditions related to *Doshic* imbalances. Additionally, poppy seeds help pacify general complaints such as thirst, fever, inflammation, constipation, abdominal colic, and irritation of the abdomen. [14] Rich in essential minerals like iodine, manganese, zinc, magnesium, and copper, they serve as natural elemental supplements. Recent studies have highlighted the significant presence of linoleic acid in poppy seeds, which is beneficial in preventing heart disorders and alleviating chronic abdominal discomfort. [15] Overall, poppy seeds offer a wide range of health benefits, contributing to both physical and mental well-being.

Properties of *Kalinda* or watermelon

Watermelon is widely recognized as a cooling, nourishing, and healing fruit. Its primary benefits include hydrating the body, cleansing and eliminating impurities, making it an excellent fruit for overall detoxification. [16] It is particularly useful in relieving conditions such as inflammation, fatigue, excess thirst, oedema, kidney infections, painful and scanty urination, and bladder infections. [17] As a natural diuretic, watermelon promotes the healthy elimination of waste and fluid from the body. Watermelon is sweet in taste and has a cold (*Sheeta*) potency, making it an effective remedy for balancing excess heat in the body. Watermelon nourishes all bodily tissues (*Santarpana*), improves strength (*Balya*) and increasing overall nutrition (*Pushti Vivardhana*). Watermelon is a source of dietary lycopene which is a lipophilic carotenoid having potent anti-oxidant and neuroprotective properties [18] was also found to be beneficial in elderly women. [19] It also has antidiabetic activity also promoting vascular function [20] hence can be prescribed in ischemic heart disease and in diabetic patients as well. [21] The high citrulline level promotes the plasma arginine percent supporting the vascular function and oxygenation of the muscular tissues making watermelon suitable for as a food first intervention in patients with dehydration and/or fatigue. [22], [23]

Discussion on network pharmacology of *Mishi Paanak*

The network pharmacology approach was also adopted to gauge for common phytochemicals and gene targets of the contents of the drink and their impact on the dehydration genes and cellular pathways of dehydration. This was done to identify whether the choice of ingredients can contribute to the prevention and management of the intense heat related and dehydration related complaints. This approach is helpful in understanding the mode of action of novel and/or processed recipes and synergistic action of the ingredients of the recipe especially for those recipes which are not directly mentioned in the Ayurveda texts. This is important to scientifically validate the traditional wisdom and understand the mode of action of this novel recipe, a network pharmacology-based approach was adopted. This approach is particularly valuable because *Mishi Paanak* is not directly described in classical Ayurvedic texts, allowing for an in silico understanding of its pharmacological characteristics and potential synergistic actions. The objective was to identify common phytochemicals, gene targets, and pathways

implicated in the management of dehydration and summer-related heat disorders. However, the targets for each of the phytochemicals involving all the three contents of the recipe was done. The most common phytochemicals and gene targets were studied in this article to assess whether the recipe would be beneficial in reducing the condition of dehydration. Using Swiss Target Prediction and Gene-Cards, the study identified 65 overlapping genes between the 20 major phytochemicals and dehydration-related gene sets. These genes govern key biological functions in hydration, vasodilation, electrolyte balance, and cellular repair.

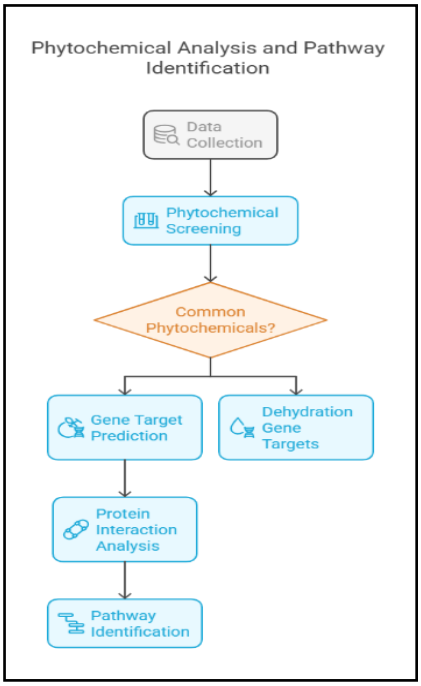

Figure No. 7: Methodology of network pharmacology followed in *Mishi Paanak* recipe

The mechanistic insights and reported gene targets for the common phytochemicals in the recipe along with the mechanism of action of cooling activity of recipe for key phytochemicals and gene targets are presented in Table No. 4 and Table No. 5 respectively.

Table No. 4: Reported gene targets and activities of the identified phytochemicals

Phytochemical	Reported Activities	Mechanistic Insights / Gene Targets
Quercetin [24]	Anti-inflammatory, antioxidant, vascular protection	Targets AKT1, PPARG, EGFR. Modulates MAPK/PI3K pathways, reducing oxidative stress and promoting vascular health, critical in heat stress and dehydration recovery.
Kaempferol [25]	Anti-oxidative, cardioprotective	Modulates ESR2, MMP2, MMP9; supports cellular hydration, membrane integrity, and reduces inflammatory signalling in hot conditions.
Linoleic and Linolenic acid [26]	Maintain skin hydration, anti-inflammatory	Influence PPARG, EGFR, aiding in barrier protection and reducing trans-epidermal water loss.
Thiamine [27] (Vitamin B1)	Energy metabolism, cognitive function	Supports IGF1R, KDR, enhancing cellular energy restoration and neuroprotection during dehydration.
Stigmasterol, β-Sitosterol [28]	Adaptogenic, cholesterol-lowering	Interact with SRC, AKT1, providing membrane stability and heat tolerance.
Limonene [29]	Gastroprotective, anti-stress	Targets AKT1, reducing oxidative stress and fatigue.

Mechanism of action for cooling property of the recipe for key phytochemicals and gene targets is mentioned in table no. 5

Table No. 5: Mechanism of cooling through the key action of phytochemicals and gene targets

Sr. No.	Proposed mechanism	Key action of phytochemicals and genes
1.	Sensory and Thermoregulatory Modulation via TRP (Transient Receptor Potential (TRP) Channels	Kaempferol and Quercetin activate TRPM8 (menthol receptor), a cold-sensing ion channel, resulting in a perceived cooling sensation on the tongue and skin.[30] Limonene, found in fennel, interacts with TRPA1 and TRPV1, indirectly inhibits heat perception by modulating nociceptive signaling. [30]
2.	Vascular Modulation for Peripheral Cooling (phytochemicals enhance microcirculation aiding in heat dissipation)	Citrulline increases plasma arginine, which serves as a precursor to nitric oxide (NO) — a vasodilator that enhances cutaneous blood flow, helping the body shed excess heat. Polyunsaturated fatty acids (PUFAs) like linolenic and linoleic acid regulate PPARG and EGFR, improving epidermal hydration and barrier function, which reduces trans-epidermal water loss (TEWL). [31]
3.	Anti-inflammatory and Antioxidant Pathways	Quercetin, Kaempferol, and Stigmasterol target AKT1, MMP2, and MMP9, modulating inflammatory pathways like NF-κB and PI3K/Akt. [32] Beta-sitosterol and Stigmasterol regulate corticosteroid-like activity, promoting a calming, cooling internal environment by reducing systemic stress. [32]
4.	Hydration and Electrolyte Restoration	Riboflavin, Thiamine, and Folic acid improve cellular metabolism and ATP production, mitigating fatigue associated with heat. [33]
5.	Neuroendocrine Influence on Heat Perception	Nicotinic acid (niacin) influences dopaminergic and cholinergic systems, reducing heat-related discomfort and fatigue. [34] Poppy seeds may exert mild GABAergic effects (from trace alkaloids), promoting relaxation, aiding in cooling perception, and reducing the stress associated with heat.
6.	Electrolyte modulation	Electrolyte balance is facilitated via PPARG and IGF1R pathways that regulate fluid retention and tissue hydration. [35]

Mechanism of action of individual genes:

The proposed mechanism of action of individual genes is presented in table no 6 as shown below [36]

Table No. 6: Mechanism of action of individual genes

Name of gene	Mechanism of action of the individual genes
KDR(VEGFR2)	Plays a key role in vascular permeability and vasodilation, enabling heat dissipation through increased skin blood flow—a key mechanism in physiological cooling.
PPARG and EGFR	Both genes regulate epidermal barrier function, hydration, and anti-inflammatory responses, which are crucial for managing heat-induced skin stress.
AKT1 and IGF1R	Involved in cell survival and stress adaptation pathways, especially under heat shock and fluid imbalance
ESR2 (Estrogen Receptor Beta):	Regulates thermosensitive responses, especially in females, and has been implicated in cooling sensations during hormonal fluctuations (e.g., menopausal hot flushes).

The combination of ingredients in *Mishi Paanak* demonstrates a clear synergistic effect, both chemically and biologically. Phytochemical analysis revealed 20 common compounds shared across the three ingredients, including well-known bio-actives such as quercetin, kaempferol, linoleic acid, linolenic acid, nicotinic acid, and thiamine. These phytoconstituents do not act in isolation; rather, they target multiple overlapping gene networks that are central to thermoregulation, inflammation, fluid balance, and cellular stress responses. For instance, quercetin and kaempferol modulate anti-inflammatory pathways via AKT1 and MMP9, while linoleic and linolenic acids influence epidermal hydration and membrane stability through PPARG and EGFR signaling. The proposed mechanisms stated in table No. 7 suggest that these synergistically produce both the perceived sensation of coolness and physiological regulation of body temperature**,** making it an effective Ayurveda-based strategy for managing summer heat. The network pharmacology analysis further supports synergy by demonstrating convergence on key biological targets. The 65 gene targets common to both the phytochemicals and dehydration-related genes were not uniformly derived from a single plant source; rather, they resulted from the collective presence of phytochemicals across all three botanicals, indicating a polyherbal synergy. Importantly, hub genes such as KDR, AKT1, PPARG, ESR2, and IGF1R were identified through Cytoscape and Cytohubba analyses, which are involved in critical pathways for vasodilation, fluid retention, hormonal modulation, and skin hydration. These shared gene interactions and overlapping functional pathways reveal that the multi-ingredient formulation is more than the sum of its parts—it leverages synergistic phytochemistry to create a broader and more effective physiological response to heat stress and dehydration.

Since molecular docking primarily focuses on the interaction between individual phytochemicals and target proteins, and our study evaluates the activity of the whole formulation as a composite entity, molecular docking of individual phytochemicals falls beyond the scope of this study.

4. LIMITATIONS

While the current network pharmacology analysis provides valuable insights into the potential mechanisms and therapeutic targets of the formulation, it remains primarily a hypothesis-generating approach. The predictive nature of this in silico method does not confirm the actual pharmacodynamic or pharmacokinetic effects of the formulation in biological systems. Specifically, in the context of conditions such as dehydration, the inferred bioactivities and molecular interactions derived from computational modelling require rigorous experimental validation.

To substantiate the proposed mechanisms and evaluate the therapeutic efficacy of the formulation, well-designed in vivo studies using relevant animal models are essential. These studies would help assess the formulation's safety profile, bioavailability, and physiological impact under dehydrated conditions. Furthermore, clinical trials are ultimately necessary to determine its effectiveness, optimal dosage, and potential side effects in human subjects. Only through such experimental and clinical validation can the

formulation's utility in managing dehydration be scientifically confirmed and potentially translated into clinical practice

The nutritional profile, analytical (GCMS or LCMS based analysis), shelf-life analysis and physico-chemical analysis of the *Mishi Paanak* drink is not done in the present study. This study is directed towards justifying the conceptual framework and rationales involved in development of Ayurveda recipes like Mishi Paanak and access their cooling effect on the system. Further studies based on GCMS OR LCMS analysis can further substantiate the findings. In the network pharmacology study, the ADMET study of all the phytoconstituents of each of the ingredients can be done which may also reveal the other pathways and mode of action of the recipe. Molecular docking study is also not under the purview of present study as docking mainly focuses on activity of the single phytochemical, in depth quantitative analysis will be required to understand the abundance. Further analysis can be done to validate the same.

5. CONCLUSION

Mishi Paanak is a natural Ayurveda-inspired summer coolant designed to combat the effects of excessive heat and dehydration during *Grishma Ritu*. By incorporating cooling and nourishing ingredients such as fennel seeds, poppy seeds, watermelon juice, and natural sweeteners, this beverage helps restore hydration, balance *Pitta dosha*, and prevent heat-induced fatigue. Its easy preparation, affordability, and health benefits make it a practical and effective alternative to commercially available highly aerated and sugar dense drinks. By integrating *Mishi Paanak* into daily dietary routines, individuals can stay refreshed, energized, and maintain overall well-being during the hot summer months. The network pharmacology of the contents of the *Mishi Paanak* also suggests that this combination of herbs and drink prepared from them has impact on the dehydration pathways also helpful in management of summer related conditions. In summary, the formulation of *Mishi Paanak* is novel both in its design and scientific validation, and it demonstrates clear synergistic effects at the molecular level that justify its use as an effective Ayurvedic summer coolant.

Abbreviations:

ADME= Absorption, Distribution , Metabolism , Excretion

ATP= Adenosine triphosphate

KDR = Kinase Insert Domain Receptor (VEGFR2)

ESR2 = Estrogen Receptor 2 (ERβ) or Estrogen Receptor Beta

AKT1 = AKT Serine/Threonine Kinase 1

IGF1R = Insulin-like Growth Factor 1 Receptor

MMP9 = Matrix Metallopeptidase 9

PTK2 = Protein Tyrosine Kinase 2 (FAK)

SRC = SRC Proto-Oncogen

MMP2 = Matrix Metallopeptidase 2

MMP9= Matrix metalloproteinase-9

PPARG = Peroxisome Proliferator Activated Receptor Gamma

EGFR1929 = EGFR variant (possibly p.L858R or other ID)

SRC = SRC Proto-Oncogene

RRDR = Regional Raw Drug Repository

IMPATT 2.0 =

Indian Medicinal Plants, Phytochemistry and Therapeutics 2.0

SMILES = Simplified Molecular Input Line Entry System

BBB = Blood Brain Barrier

KEGG = Kyoto Encyclopedia of Genes and Genomes

MF = Molecular functions (MF)

BP= biological processes

CC= cellular components

P_{adjj} = adjusted p-value

MAPK= mitogen-activated protein kinase

PI3K = Phosphoinositide 3-kinases

TRP= Transient Receptor Potential

NO= nitric oxide

TRPM8 = Transient Receptor Potential Cation Channel Subfamily M Member 8

TRPA1 = Transient Receptor Potential Vanilloid 1

TRPV1= Transient receptor potential ankyrin 1

PUFA= Polyunsaturated fatty acids

TEWL = Trans-epidermal water loss

NF-Kb= Nuclear factor-κB

GABA= Gamma-aminobutyric acid

VEGF = vascular endothelial growth factor

GCMS = Gas Chromatography-Mass Spectrometry

LCMS= Liquid Chromatography-Mass Spectrometry

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