



Review Article

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EXPLORING THE ROLE OF *TIKTA RASA* (BITTER TASTE) THROUGH BIO-SIGNALING PATHWAYS IN TARGETED TREATMENT OF TYPE II DIABETES MELLITUS: A REVIEW

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ABSTRACT

Type II Diabetes Mellitus (DM) is one of the diseases in triad of metabolic syndrome with latest statistics of prevalence rate in India being 62 million. In the same context, Charak Samhita explains causes of *Santarpanjanya vyadhi* (metabolic disorders) which includes *Prameh* (DM) and advocates predominant use of herbs possessing *Tikta Rasa* (bitter taste) in *Shodhan* (body detoxifying) treatment. But the exact understanding of perception of *Tikta Rasa* through bio-signaling pathways on cellular receptor levels still remains unexplored. To comprehend this concept, the exact mechanism of perception of *Tikta rasa* through gustatory receptors and intestinal chemo sensory cells stimulating bio-signaling to the brain and periphery mediated via G-Protein Coupled Receptors (GPCRs) role of the latter in the post prandial control of metabolism requires a detailed enquiry. This could possibly pave the way of understanding the pathway of perception and actions of *Tikta rasa*. In this review article, Ayurvedic texts and websites have been documented precisely which includes literature review of *Rasa* and bio-signaling pathways. Literature studied is suggestive of mode of action of *Madhur* (Sweet taste) & *Tikta rasa*, which is carried through GPCRs mediated through gustatory and metabolic function. *Atiyog* (excess) of *Madhur Rasa* causing metabolic disorder (Type II DM) followed by its treatment by *Tikta Rasa* has been explained. This review is a comprehensive learning of probable mode of action of *Tikta Rasa* through bio-signaling pathways thereby, emphasizing the targeted treatment in Type II DM, which has been already stated in Ayurveda.

Keywords: *Madhur Rasa*, *Tikta rasa*, Type II Diabetes mellitus, G- Protein Coupled Receptors, Bio signaling pathways.

INTRODUCTION

The purpose of the five senses serves to afford an assessment of the nature of the immediate environment to human beings. Among these five senses, one such sense organ is tongue which recognizes the *Rasa* (taste). *Rasa* is the taste appreciation of the substance by the chemical receptors on the tongue. *Rasa* is *Panchabhautik* (composed of five elements) in nature which involves *Jal Mahabhut* (water element) as a predominate one¹. The concept of *Rasa* has long been the object of study. This concept is found to be much developed in Ayurveda and recently, chemical nature of the same has been the field of further research. Recent research on Taste recognition chemistry suggests that tastes are initiated by chemical recognition reactions with the receptor that are transmitted through water which has been long back mentioned in Ayurveda². Ayurveda recognizes 6 *Rasas* (6 Principal Tastes) out of which excessive intake of *Madhur Rasa*, is one of the chief reasons known to cause *Santarpanjanya Vyadhi*³ which in modern text can be quoted under Metabolic Syndrome, defined as a cluster of biochemical and physiological abnormalities associated with the development of cardiovascular disease and type II DM⁴. While discussing about the treatment of Type II DM which is one of the disease manifestation in *Santarpanjanya Vyadhi*, it is important to understand the physiological process of cell and its working through bio signaling pathways through G protein coupled receptors. In this meticulous study, attempt has been made to explore the causes in view of *atiyog* (excess ingestion) of *Madhur Rasa* and significance of *Tikta Rasa* in metabolic syndrome and its probable

mode of action in Type II DM through bio-signaling pathways. Moreover, this review article encompasses the literary review through the knowledge of Traditional system of Medicine of Ayurveda with relevant information from published research articles available on internet focusing Cell signaling mechanism, G-PCRs in Type 2 DM with an overview to *Madhur* (Sweet) & *Tikta* (Bitter) *Rasa* (Taste); its Bio-signaling through G-PCRs, Concept of *Raso Nipate Dravyanam* (Action of Herbs through Taste Recognition) with reference to *Madhur & Tikta Rasa*, Bio-signaling aspects of *Santarpanjanya vyadhi* (Metabolic Syndrome) in Type II DM and role of *Manovah Srotas* (Mind) with special reference to Defect in Bio-signaling Pathway in Type II DM.

Cell Signaling Mechanism

Our body cells are composed of bi-lipid membrane which is embedded with thousands of receptors made up of proteins. These receptor proteins carry out specialized functions to help us lead active healthy life through the bio-signaling pathway or Signal Transduction. The science of epigenetics today states that signal transduction pathways lies between the membrane's reception of environmental signals and activation of the cell's behavior proteins. All cellular responses are as a result of external or environmental factors⁵. The signals transmitted to the cell via receptor proteins from external environment help the cell for its optimum working and the derangement in signaling or over signaling leading to disease state of the cell causing diseases such as cancer, autoimmunity and diabetes⁶.

Concept of G-Protein Coupled Receptors in Type 2 Diabetes Mellitus

G-Protein Coupled Receptors (G-PCRs) are group of protein receptors on the bi-lipid cell membrane that are responsible to carryout functions of metabolism, immune response and brain function. G-PCRs exert its action by attaching to naturally occurring substances called as ligands which are present outside the cell. A ligand is a substance that forms a complex with a biomolecule to serve a biological purpose⁷. With the lock and key arrangement of the ligand – receptor complex, every time this channel revolves, it shuttles three positive charged sodium atoms out of the cytoplasm and simultaneously admits two positive charged potassium atoms into the cytoplasm from the environment⁸. The binding of ligands with their respective receptor typically results in a change of conformation of the target protein. When these ligands bind with G-PCRs, it causes G-PCRs to change shape allowing the G-PCRs to transmit signals inside the cell.

Overview to *Madhur* (Sweet) & *Tikta* (Bitter) *Rasa* (Taste)

Sweet taste provides a sense of compassion and satisfaction due to presence of sugar which forms the main source of energy. Foods rich in simple carbohydrates are those most commonly associated with sweetness⁹. A number of plant produce glycosides that are sweet at concentration example being glycyrrhizin from *Yashtimadhu*. On the contrary, we have a natural aversion for bitter taste as it is not palatable. It causes numbness of gustatory cells and hence, after tasting bitter taste no other taste can be perceived immediately thereafter¹⁰. In that case, it is interesting to understand why plants themselves turn bitter. As stated earlier, as beings have aversion towards this taste, herbivores usually avoid eating bitter tasting plants and hence, in plants bitter taste forms the defense mechanism for them. Moreover, most of the bitter tasting compounds also play a role of defense mechanism in humans as poisonous content within the plant also taste bitter. The bitter tasting phytochemicals in plants include phenols, terpenoids, alkaloids, flavonoids, glucosinolates and isothiocyanates¹¹.

Bio-signaling Aspect of *Madhur Rasa* (Sweet Taste) through G-PCRs

It forms important to understand how glycosides like glycyrrhizin does are perceived by gustatory cells. As per modern taste recognition researches, sweetness is perceived via G protein coupled receptors coupled to G protein gustducin, receptors being T1R2+3 (heterodimer) and T1R3 (homodimer). Sweet tasting ligands bind to these receptors and activate G protein, gustducin which in turn activates adenylate cyclase. Adenylate cyclase catalyzes the conversion of ATP to cAMP. The cAMP molecule then activates a protein kinase, which in turn phosphorylates and doses a potassium ion channel. The excess potassium ions increase the positive charge within the cell causing voltage gated calcium ion channels to open, further depolarizing the cell. The increase in Calcium ultimately causes neurotransmitter release, which is then received by a primary afferent neuron.^{12,13}

Bio-signaling Aspect of *Tikta Rasa* (Bitter Taste) through G-PCRs

Similar to Sweet ligands, bitter taste ligands also do bind with G-PCRs. The TAS2R proteins function as bitter taste receptors. Again via gustducin, activation of phosphodiesterase takes place with decrease cyclic nucleotide levels. Further transduction pathway still remains to be explored but another exposition state that activation Inositol triphosphate (IP3) and diglyceride (DAG)

may open Ion channel with release of Calcium within the cell causing the cell to depolarize followed by perception of taste by afferent neurons.^{12,13}

Concept of *Raso Nipate Dravyanam* (Action of Herbs through Taste Recognition) with Reference to *Madhur* & *Tikta Rasa*

It has been postulated that the mode of action of *dravya* (herbs) takes chiefly through the *Rasa* of the *dravya*¹⁴ (*Rasapradhanya* of *Dravya*). In order to understand this concept, further exploration of taste transduction mechanism states that G-PCRs are found not only on the gustatory cells but also in GI tract - gastric and intestinal mucosa, respiratory system and brain but the research on G-PCRs is limited currently only till gustatory and GI tract cells. This explains us the probable mode of action of *Madhur rasa* which causes *Saptadhatuabhivardhan*¹⁵ and also in *atiyog* of *Tikta Rasa* it has been stated to cause *Saptadhatushoshan*¹⁶ as GPCRs are present almost all over the body. Moreover, literary study in taste transduction states that, G-PCRs in gustatory cells helps in discrimination of food whereas G-PCRs in GI tract – gastric and intestinal mucosa act as chemosensors for utilization of nutrients and appetite regulation¹⁷. This theory does explain that *Tikta Rasatmak dravya* (Bitter taste ligands) on binding with G-PCRs of gustatory cells produce numbness of oral cells in order to discriminate poisonous food if any; whereas the same ligands on binding with GI tract GPCRs helps to improve the appetite. Furthermore, G-PCRs are also known to be mediated by gut - brain – pancreatic axis through GLP1 receptor chiefly being the object of further research of therapeutic efficacy in Type 2 DM and obesity¹⁸.

Bio-signaling Aspects of *Sanatarpanjanya vyadhi* (Metabolic Syndrome) in Type II DM

An excess of ligand causes defect in GPCR leading to over-signaling within the cell causing Type 2 Diabetes. Excess of ligands has been rightly mentioned in Charak Samhita sutrasthan that excess amount of food tasting *Madhur Rasa*, *Snigdha* (oily in consistency) and *Guru* (heavy to digest) are the chief reason for all *santarpanjanya vyadhi* one being Type 2 DM¹⁹. As Type 2 DM is Insulin resistant, this can be explained by the conformation of GPCRs thereby causing deranged or over signaling to the cell causing no uptake of decreased uptake of sweet tasting ligands. This accumulation of ligands over GPCRs causes the body to sense post prandial high sugar level which is a finding in Type 2 DM.

Role of *Manovah Srotas* (Mind) w.s.r. to Defect in Bio-signaling Pathway in Type II DM

Though not being in the purview of this article as it is primarily aimed at focusing the significance of *Tikta Rasa* in Type II DM, the role of *Manovah srotas* (stress) forms an integral aspect to discuss while discussing the causes of the disease. While explaining the role of stress in Type II DM, it has been researched that the key molecules of the neural network which are metabotropic glutamate receptors (mGlu) are GPCRs as well. These mGlu receptors are chiefly responsible fear and anxiety. Importantly, the key molecules of the neural network, which are the metabotropic glutamate receptors (mGlu), are also GPCRs (Nicoletti et al., 2011)²⁰ which explains the role of *Manovah srotas* as one of the causative factor of Type 2 DM. Moreover, receptors can read energy fields and hence, biological behavior can be controlled by invisible forces including thoughts²¹.

DISCUSSION

After thorough literary review, understanding cell signal transduction study allows us to acquire the knowledge of binding of specific ligands to their respective receptors. When we study the pathology of Type 2 DM through cell signal transduction study, G protein coupled receptors are the receptors involved in the uptake of Insulin, followed by utilization of glucose molecules. Moreover, Sweet tasting ligands and Bitter tasting ligands are also perceived via G protein coupled receptors. These GPCRs are not only present on the gustatory cells but also in GIT tract – intestine (known as chemosensory cells), pancreas and brain. Out of these sites, extensive research on GI tract chemo sensation has been studied which states that oral GPCRs are chiefly responsible for taste whereas other GI tract GPCRs are responsible for appetite regulation. This draws the supposition that the *atiyog* (excess intake) of *Madhur Rasa* that is excess of ligands of sweet taste causes alteration or excessive signaling in transduction causing inflammation within the cell, thereby disrupting its physiological function leading to *Agnimandya* (decreased tissue metabolism). As *Tikta Rasa* is composed of *Vayu* (Air) & *Aakash* (ether) *Mahabhut* (element) as predominant elements thereby, consisting of *laghu* (light in weight), *ruksha*²² (causing dryness) and *lekhan* (scraping property) itself, it helps in correction of this bio- signaling pathway by clearing the *margaavrodh* upon the cell (obstacle to nutrient transport and information transfer upon the cell membrane) which probably could be clearing the obstruction of signal transduction pathway, thereby further causing the uptake of sweet ligands by the cells²³ and also possibly through correction of conformation of GPCRs. While further exploring the treatment of *Santarpanjanya vyadhi*, it has been advocated to go for *shodhan chikitsa* which comprises maximum *Tikta Rasatmak dravya* again due to its deep penetrating activity in *srotasas* (channels) owing to *Vayu & Aakash Mahabhut*. This makes us understand the importance of *Tikta Rasa* in treatment of Type 2 DM. Moreover, Current research on bitter taste states that, bitter ligands activate TAS2R38 – GPCR which in turn helps to release gut peptides of enteroendocrine L-cells in vitro. Release of these peptides has a therapeutic efficacy for Type 2 DM²⁴. The study still being under research but forms the basis of mode of action of *Tikta Rasa* in treatment of type 2 DM.

CONCLUSION

It is very much evident from the present conceptual review work that for the purpose of treatment of Type 2 DM which is one of the triad of metabolic syndrome, *Tikta Rasa* forms the integral part and hence, for targeted treatment of type II DM exploration of the role of *tikta rasa* through bio – signaling pathways is of utmost importance which has been long time back postulated in Ayurvedic classical texts. Thus, it is important to understand the significance of *Madhur Rasa* in view of causative factors and *Tikta Rasa* while planning the treatment protocol of Type II DM. Herbs or formulations containing herbs from *Tikta Gana* (group of bitter herbs) like *Patola* (*Luffa acutangula*), *Ushir* (*Vetiveria zizanioides*), *Chandana* (*Santalum album*), *Bhunimba* (*Andrographis paniculata*), *Nimb* (*Azadirachta indica*), *Katuka* (*Picrorhiza kurrooa*), *Tagara* (*Valeriana officinalis*), *Kutaj* (*Holarrhena antidysenterica*), *Karanja* (*Pongamia pinnata*), *Haridra* (*Curcuma longa*), *Daruharidra* (*Berberis aristata*), *Musta* (*Cyperus rotundus*), *Murva* (*Marsdenia tenacissima*), *Vasa* (*Adhatoda vasica*), *Patha* (*Cissampelos pareira*), *Apamarga* (*Achyranthes aspera*), *Guduchi* (*Tinospora cordifolia*), *Dhanvyaas* (*Fagonia cretica*), Herbs from *Bruhatpanchmool* (Roots of five following big trees) – *Bilva* (*Aegle marmelos*), *Agnimantha* (*Premna integrifolia*), *Shyonaka* (*Oroxylum indicum*), *Patala* (*Stereospermum suaveolens*),

Gambhari (*Gmelina arborea*), *Ativisha* (*Aconitum heterophyllum*) and *Vacha* (*Acorus calamus*) needs to be incorporated for effective management of the disease. Apart from that, role of these herbs and its mode of action in *Panchkarma* (body detoxification processes) in Type II DM leaves us with further scope of study in the subject.

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