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# Molecular Mechanism of Nishamalaki as Rasayana in Diabetes Mellitus

**Research Article**

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## Abstract

Diabetes mellitus, a chronic non-communicable disorder, is on the rise in developing countries. In Ayurveda, a similar condition called *Madhumeha* is attributed to *Dhatu kshaya* (Emaciation) and *Dosha avarana* (occlusion of humoral factors). *Rasayana* therapy, involving herbal formulations like *Nishamalaki*, is recommended to strengthen the body's major structural components (*dhatus*), boost immunity, and promote longevity. *Nishamalaki*, a combination of *Haridra* (*Curcuma longa* Linn.) and *Amalaki* (*Phyllantus emblica* Linn.), exhibits antioxidant, anti-inflammatory, and lipid-reducing properties. It holds potential as a preventive measure to enhance the Quality of Life. The aim of this study was to validate the rejuvenation property of *Nishamalaki* in Diabetes mellitus using an insilico approach. Through tools such as SwissADME, SwissTargetPrediction, and Therapeutic Target Database (TTD), bioavailable components of *Nishamalaki* and Diabetes were analyzed, and a network was created using CytoScape. The results of the study identified two key compounds, Ellagic acid and Corilagin, which significantly modulate IGF1R and PTPN1, respectively, in Diabetes mellitus. These findings offer valuable insights into the potential therapeutic benefits of Nishamalaki in managing Diabetes mellitus and warrant further research and exploration in this area.

**Keywords:** Diabetes mellitus, *Rasayana, Nishamalaki, Haridra, Amalaki,* Ellagic acid, Corilagin, IGF1R, PTPN1.

## Introduction

Diabetes mellitus is a chronic non-communicable disease that contributes significantly to the burden of Disability-adjusted life years, according to a WHO health estimate. Developing countries have experienced a worrying surge in the prevalence of diabetes, with figures rising from 108 million affected individuals in 1980 to 422 million in 2014. In 2019 alone, 1.5 million deaths were attributed to this disease.(1) Uncontrolled diabetes can lead to major organ failure, including the kidneys and heart, as well as blindness.(2) In Ayurveda, diabetes is referred to as *Madhumeha* and is thought to be caused by either *Dhatu kshaya* (Emaciation) and *Dosha avarana* (occlusion of humoral factors).(3) To prevent the progression of this condition and reduce future complications, *Rasayana* (Rejuvenation) therapy is considered essential in cases of emaciation.

Building on the concept of *Ayurvedic* medicine as a holistic approach to wellness, we will explore the principles of Rejuvenation therapy. *Ayurveda* has advocated the importance of maintaining the well-being of a healthy person and treating the disease of a sick person.(4) In order to achieve this, Rejuvenation therapy has been recommended, which contains dedicated herbs and formulations, diets, regimes, and etiquettes. Rejuvenation therapy, along with the treatment of disease, enables strengthening the disease-battling power to achieve faster and better relief.(5) Based on various research carried out, it can be inferred that these help in promoting *Ayu* (Life span), *smriti* (Memory), *medha* (Intelligence), *taruna vaya* (Natural aging), etc. by stimulating telomerase activity, DNA repairing, and reducing oxidative stress-induced changes.(6)

One such formulation is *Nishamalaki* (NA). NA is a formulation containing Turmeric and Indian Gooseberry. It is manufactured by triturating powdered Turmeric (*Curcuma longa* Linn.) with fruit juice of Indian Gooseberry (*Phyllantus emblica* Linn.).(7) Hence, it is easy to prepare and economial compared to polyherbal formulations. This combination, along with honey, is said to pacify *Prameha* (obstinate urinary disease), a classification of diseases mainly related to the urinary system.(8)(9) Recent studies have revealed the capacity of Turmeric to reduce the levels of free fatty acids, serum cholesterol, triglycerides, and Low-density lipoprotein (LDL) while simultaneously increasing the level of High-density lipoprotein (HDL) cholesterol. It has also been proven effective in reducing blood glucose levels and thwarting the development of abdominal fat mass.(10) Similarly, Indian Gooseberry has shown significant results in reducing lipid and blood glucose levels.(11)

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## Materials and Methods

The present study obtained information on NA and its constituent drugs for treating diseases through a thorough review of relevant literature and various databases. The construction of the NA-docking network involved the utilization of pertinent databases and applications.

Mining of phytoconstituents of Indian Gooseberry and Haridra and proteins involved in Diabetes

The phytochemicals present in the fruit of Indian Gooseberry (*Phyllantus emblica* Linn.) and rhizome of Turmeric (*Curcuma longa* Linn.) were sourced from the Dr. Duke's Phytochemical and Ethnobotanicals database.(12) Structural information of these phytochemicals was obtained through the Pubchem database.(13) In order to identify the proteins that play a role in Diabetes mellitus, known targets of this disease were referenced from Gene cards.(14) Subsequently, the Gene IDs of each protein molecule that was identified as a Diabetes mellitus target were retrieved from UniProt.(15)

### Analysis of Drug-likeness property of Phytochemicals and their targets

To identify suitable phytochemicals for further analysis, Molsoft software was utilized to screen for those that comply with Lipinski's rule and have good druggability scores. The selected phytochemicals were then subjected to target identification using the SwissTargetPrediction(16) database. This process ensured that only "druggable" phytochemicals with potential therapeutic value were included in subsequent analysis.

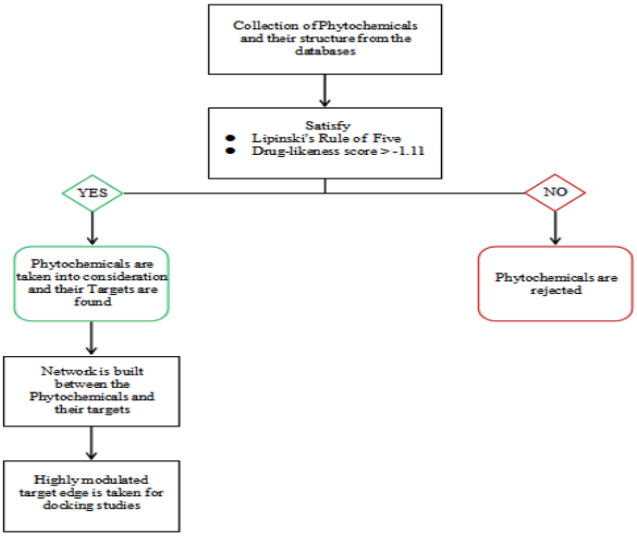
### Pathway and network analysis

To gain insight into the potential therapeutic effects of the identified "druggable" phytochemicals in Diabetes mellitus, sets of proteins involved in this disease were queried in STRING.(17) Gene enrichment analysis was performed to identify the pathways that are modulated by the phytoconstituents, and further KEGG(18) pathway analysis was conducted to determine the specific pathways involved in Diabetes mellitus. The Cytoscape software was employed to construct a network that encompasses the phytoconstituents, protein molecules, and identified pathways.(19) Node size and color were used to interpret the network, with the size of nodes reflecting the number of edges and the color indicating the degree of connectivity. This analysis enabled a comprehensive understanding of the potential mechanisms underlying the therapeutic effects of the identified phytochemicals in Diabetes mellitus.

### Docking studies

To investigate the potential binding of the identified phytoconstituents with the Insulin-like growth factor 1 receptor (IGF1R) and Tyrosine-protein phosphatase non-receptor type 1 (PTPN1) receptor, three-dimensional structures of the phytoconstituents were retrieved from the PubChem database. Similarly, the target molecules for IGF1R and PTPN1 were obtained from the RCSB(20) database viz. 2OJ9 and 1Q6P respectively, and water molecules and heteroatoms were removed from the protein molecules through Discovery Studio.(21) PyRx software(22) was used to perform docking studies and obtain the binding affinity of the phytoconstituents with 2OJ9 and 1Q6P. The lowest binding energy was chosen based on scoring, and the ligand-protein interaction was visualized to gain insight into the potential molecular mechanisms underlying the therapeutic effects of the identified phytochemicals in Diabetes mellitus.

**Figure 1: Flow-chart illustrating Methodology**




## Observations and Results

Throughout the analysis, only phytoconstituents that meet the specified criteria were selected for subsequent steps. In the final step, a total of 11 constituents of *C. longa* Linn., were considered for further analysis. Similarly, Ellagic acid, Gallic acid, and other constituents of *P. emblica* Linn. were also taken into account in the final selection. This rigorous selection process ensured that only the most promising phytoconstituents were included in subsequent analyses.

**Table 1: Number of Phytochemicals considered for further process**

| | Name of the databases and applications | | | | |
|---|---|---|---|---|---|
| **DRUG** | **Dr. Duke's phytochemical and Ethanobotanical database** | **PubChem** | **Molsoft** | **SwissTargetPrediction** | **Cytoscape** |
| ***C. longa* Linn.** | **94** | **63** | **11** | **11** | **11** |
| ***P. emblica* Linn.** | **24** | **19** | **7** | **7** | **7** |

**Table 2: Phytochemicals of NA used in Cytoscape**

| S.No | Phytochemicals of *C. longa* Linn. | Phytochemicals of *P. emblica* Linn. |
|---|---|---|
| 1 | Curcumin | Ellagic acid |
| 2 | Cyclocurcumin | Gallic acid |
| 3 | Curcumenone | Ethyl gallate |
| 4 | Curzerenone | Myristic acid |
| 5 | Procurcumenol | Corilagin |
| 6 | Caffeic acid | Phyllantidine |
| 7 | Campesterol | Gibberellin-A-1 |
| 8 | Turmeronol-A | |
| 9 | Turmeronol-B | |
| 10 | Bisabola-3,10-dien-2-one | |
| 11 | Quercetin | |

Upon discerning the network obtained from our analysis, it was found that 18 phytochemicals present in NA interacted with specific proteins in various permutations and combinations. These proteins play pivotal roles in distinct biological functions, and their disruption can lead to the manifestation of disease symptoms. However, the bioactive components of the NA compound drug, upon interacting with the compatible proteins, exhibit the ability to restore normalcy or even enhance their functions. The identified pathways involved in these interactions include the following:

**Figure 2: A Network depicting relation between Phytochemicals of *P. emblica* Linn. and *C. longa* Linn.with their target genes**

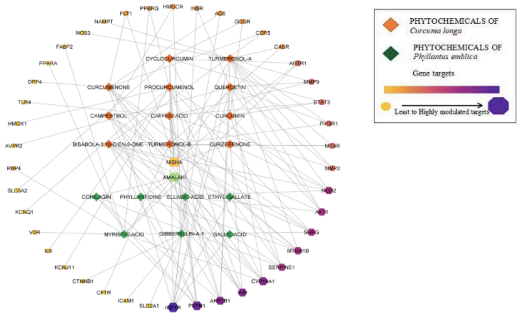



**Figure 3: A Network depicting interaction of Target with their pathways**

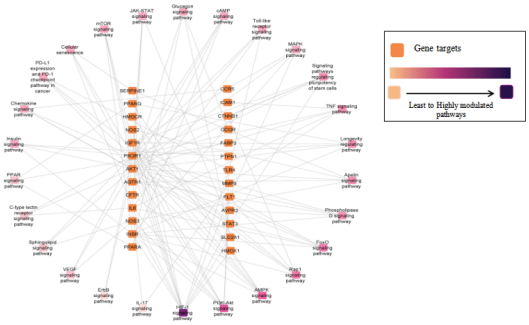



**Table 3: Pathways through which NA coordinates its actions and their Physiological functions**

| S.No | Pathways | Physiological Function | Number of Genes involved |
|---|---|---|---|
| 1 | AMPK signaling pathway | Senses for metabolic stress in cells. Also regulates appetite, energy expense among others. (23)<br>In mammals, Coordinates growth and metabolism especially the liver, muscle and fat.(24) | 7 |
| 2 | Apelin signaling pathway | Functions include increasing heart contraction;vasodilation;maintains homeostasis of glucose and insulin ; cardiovascular development, etc.(25) | 5 |
| 3 | cAMP signaling pathway | Responsible for immune function ,metabolism,gene regulation, and memory(26) | 4 |
| 4 | Cellular senescence | Defense mechanism to prevent damage due to different types of stress. Also responsible for Aging and related diseases.(27) | 4 |
| 5 | Chemokine signaling pathway | Guides lymphocytes throughout the body as defense mechanism through chemokine signals.(28) | 4 |
| 6 | C-type lectin receptor signaling pathway | Provide Innate immunity through pattern-recognition receptors (PRRs)(29) | 3 |
| 7 | ErbB signaling pathway | Intracellular signaling pathway that performs proliferation, differentiation and cell motility.(30) | 2 |
| 8 | Glucagon signaling pathway | Glucagon signaling is essential for maintaining the balance of glucose in the blood. It may also help in lipid metabolism.(31) | 4 |
| 9 | FoxO signaling pathway | Involved in proliferation differentiation and apoptosis of cells, as well as DNA damage and repair (32) | 6 |
| 10 | HIF-1 signaling pathway | Mediates cellular response to hypoxia to restore tissue homeostasis(33) | 13 |
| 11 | IL-17 signaling pathway | Necessary for immunity, tissue regeneration etc.(34) | 2 |

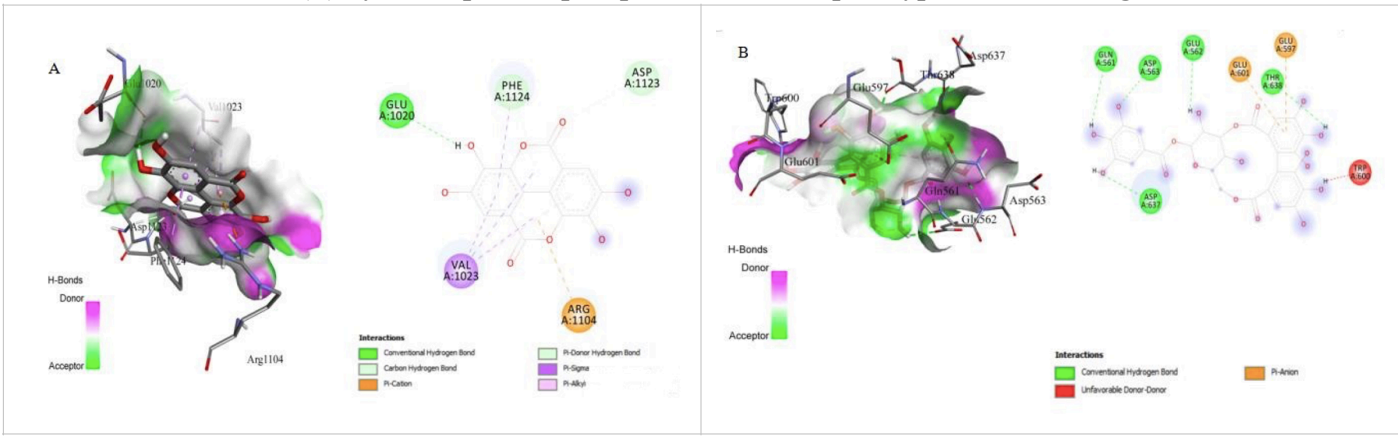
| | | | |
|---|---|---|---|
| 12 | Insulin signaling pathway | Promotes homeostasis of Glucose.(35) | 4 |
| 13 | JAK-STAT signaling pathway | Responsible for proliferation,differentiation, migration, apoptosis, and survival of cells.(36) | 4 |
| 14 | Longevity regulating pathway | Cellular competency is achieved through Autophagy, defense against stress, etc. (37) | 5 |
| 15 | MAPK signaling pathway | Relays extracellular signals across the cell membrane to the nucleus and also performs cell survival and cell death.(38) | 4 |
| 16 | mTOR signaling pathway | Performs processes required for cell growth and metabolism, functions as an integrative node for cellular nutrient and stress status and invokes suitable responses.(39) | 4 |
| 17 | PD-L1 expression and PD-1 checkpoint pathway in cancer | Important for developing Immune tolerance. Knock-out of PD-1/PD-L1 leads to auto-immunity (Lupus like arthritis, diabetes etc.) in animal models.(40) | 4 |
| 18 | Phospholipase D signaling pathway | Plays a role in maintaining cytoskeletal dynamics, membrane remodeling and cell proliferation in mammalian cells etc. (41) | 5 |
| 19 | PI3K-Akt signaling pathway | Indispensable in metabolism, growth, proliferation, and survival of cells.(42) | 8 |
| 20 | PPAR signaling pathway | PPARalpha plays a role in the clearance of lipids through the lipid metabolism of liver and skeletal muscle. PPARbeta/delta is entangled in lipid oxidation and cell proliferation while the PPARgamma promotes adipocyte differentiation to improve blood glucose consumption.(43) | 3 |
| 21 | Rap1 signaling pathway | Involved in immunological process like macrophage phagocytosis, transfer of leukocytes, lymphocyte etc. to peripheral organs, adhesion of cells to various proteins like fibronection and fibrinogen.(44) | 6 |
| 22 | Signaling pathways regulating pluripotency of stem cells | Signaling pathways needed to maintain pluripotency of stems cells.(45) | 5 |
| 23 | Sphingolipid signaling pathway | Following Genotoxic stress, Ceramide and Sphingosine initiates apoptosis, cell cycle arrest, and differentiation, whereas Sphingosine-1-Phosphate(S1P) induces proliferation, survival, and inhibition of apoptosis.(46) The balance between S1P versus Sphingosine and Ceramide and the resulting regulation of opposing signaling pathways are the crucial factors that determine survival or death of the cells.(47) | 3 |
| 24 | TNF signaling pathway | Causes necrosis of tumor, helps in regeneration of tissues, survival and proliferation of cells. It also invokes immune responses.(48) | 5 |
| 25 | Toll-like receptor signaling pathway | Recognizes pathogen-associated molecular patterns and evokes inflammatory immune response to it. This recognition of pathogens by Pattern Recognition receptors(PPRs) play a very crucial role in the generation of an effective innate immune response.(49) | 4 |
| 26 | VEGF signaling pathway | Central in vasculogenesis and angiogenesis. Also maintains choroidal health in aging and Age related Macular Degeneration.(50) | 3 |

Docking studies evaluate the interaction affinity between molecules and proteins to understand their binding behavior. However, investigating multiple targets with multiple molecules can be time-consuming and generate intricate data. Thus, we concentrated on performing docking studies with the two targets that showed the highest edge count in this investigation: Insulin-like growth factor 1 receptor (IGF1R) and Tyrosine-protein phosphatase non-receptor type 1 (PTPN1). Prior to docking, the receptors were prepared to ensure accuracy in the results. Subsequently, we docked all the phytochemicals that were found to be interacting with the identified receptors. This approach enabled us to assess the binding affinities of each phytochemical to the respective receptor.

**Table 4: Binding energy elicited by Insulin-like growth factor 1 receptor(IGF1R) and Tyrosine-protein phosphatase non-receptor type 1 (PTPN1) with their respective ligands**

| Phytochemicals | IGF1R Binding Energy (kcal/mol) | Phytochemicals | PTPN1 Binding Energy (kcal/mol) |
|---|---|---|---|
| **Ellagic acid** | **-9** | **Corilagin** | **-8.1** |
| Quercetin | -8.2 | Campesterol | -7.2 |
| Cyclocurcumin | -8.1 | Ellagic acid | -7.1 |
| Turmeronol-A | -7.5 | Procurcumenol | -6.9 |
| Gibberellin A 1 | -7.1 | Caffeic acid | -6.8 |
| Curcumenone | -6.9 | Bisabola-3,10-dien-2-one | -6.1 |
| Ethyl gallate | -6 | Myristic acid | -5.4 |
| Gallic acid | -5.8 | | |

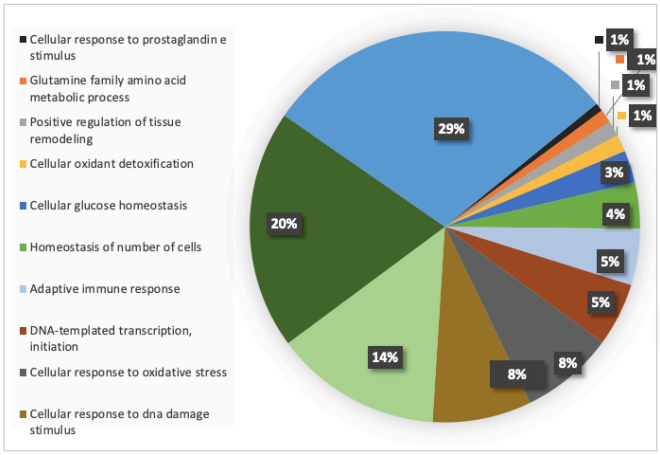
**Figure 4: 3D and 2D representation of interaction of (A) Insulin-like growth factor 1 receptor with Ellagic acid and (B) Tyrosine-protein phosphatase non-receptor type 1 with Corilagin**




## Discussion

The study revealed that the phytochemicals of NA interact with various proteins involved in insulin signaling, glucose metabolism, and inflammation pathways, thus demonstrating their potential therapeutic efficacy in managing diabetes mellitus. Some of the Biological processes provide insight into the mechanisms of action of NA and its potential as a Rejuvenation agent for diabetes management. This discussion aims to explore the interactions of Nishamalaki with key signaling pathways implicated in diabetes and its complications.

**Figure 5: Pie chart depicting percent of proteins involved in some of the Biological processes**




Few of the significant pathways from the Table 3 that might help in the rejuvenation is discussed below:

### AMPK Signaling Pathway

The AMP-activated protein kinase (AMPK) pathway serves as a cellular energy sensor, playing a fundamental role in regulating glucose and lipid metabolism. Activation of AMPK promotes glucose uptake, enhances insulin sensitivity, and inhibits gluconeogenesis and lipogenesis.(23) NA's potential to modulate AMPK activation suggests its capacity to enhance glucose utilization and potentially reduce insulin resistance. This interaction aligns with NA's traditional Ayurvedic role in promoting metabolic balance.

### cAMP Signaling Pathway

The cyclic adenosine monophosphate (cAMP) pathway is intricately involved in insulin secretion and glucose metabolism.(51) By potentially enhancing cAMP-mediated processes, NA could facilitate improved insulin secretion and cellular responsiveness to insulin, contributing to better glycemic control.

### FoxO Signaling Pathway

The Forkhead box O (FoxO) family of transcription factors plays a significant role in regulating antioxidant defenses and cellular stress responses.(32) NA's modulation of the FoxO pathway suggests its potential to augment cellular resilience against oxidative stress, a hallmark of diabetes-related complications. By enhancing antioxidant mechanisms, NA could contribute to the prevention of cellular damage and promote healthy aging.

### MAPK Signaling Pathway

Mitogen-activated protein kinases (MAPKs) are pivotal in cell growth, differentiation, and responses to stress. NA's potential impact on the MAPK pathway could extend to mitigating inflammation, a key factor in diabetes progression, and enhancing insulin sensitivity. (52) Modulating MAPKs might influence tissue repair processes and overall metabolic health, contributing to NA's potential therapeutic benefits.

### PI3K-Akt Signaling Pathway

The phosphoinositide 3-kinase (PI3K)-Akt pathway is central to insulin signaling and glucose uptake. NA's interaction with this pathway underscores its potential to enhance insulin sensitivity and promote glucose utilization.(53) By potentially amplifying PI3K-Akt signaling, NA may contribute to improved cellular response to insulin and efficient glucose transport.

### HIF-1 signaling pathway

Hypoxia Inducible Factors (HIFs) are responsible to maintain the homeostasis of oxygen at the level of tissue. The adaptive response includes promoting the expression of genes involved in angiogenesis (formation of new blood vessels), glycolysis (a cellular process for energy production), and cell survival. The

disruption of their functioning leads to complications such as diabetic foot ulcers, diabetic nephropathy, diabetic retinopathy etc.(54) Thus, intervention with NA might enhance the functioning of HIFs and improve the oxygen levels in the tissue.

**PPAR Signaling Pathway**

Peroxisome proliferator-activated receptors (PPARs) regulate lipid metabolism and insulin sensitivity.(55) NA's potential to modulate PPARs aligns with its potential to impact lipid profiles and contribute to metabolic equilibrium. Activation of PPARs could potentially lead to improved lipid regulation, making NA a candidate for addressing dyslipidemia associated with diabetes.

**mTOR Signaling Pathway**

The mechanistic target of rapamycin (mTOR) pathway is integral to cell growth, metabolism, and nutrient sensing.(39) NA's interaction with this pathway holds implications for cellular energy utilization and nutrient homeostasis. By potentially influencing mTOR activity, NA could contribute to optimized cellular growth and energy utilization, factors crucial in diabetes management.

**Sphingolipid signaling pathways**

The sphingolipid signaling pathway is a complex and multifaceted system involved in various cellular processes, including cell survival, apoptosis, cell proliferation, and stress responses. Sphingolipid signaling is influenced by cellular stress and oxidative processes.(47) NA which contains Turmeric and Indian Gooseberry, both known for their potent antioxidant and anti-inflammatory properties, may help reduce oxidative stress within cells, potentially indirectly affecting sphingolipid metabolism by reducing cellular stress.

## Conclusion

In conclusion, the bioinformatics analysis of NA has revealed its Rejuvenation properties through various pathways and its ability to induce glucose homeostasis. These findings provide evidence for the traditional use of NA as a therapeutic agent for diabetes and other age-related disorders. By validating the pharmacological actions of NA using modern tools and terminology, this study bridges the gap between traditional and modern medicine. The results obtained from this study could aid in the development of novel drugs and therapies for the treatment of diabetes and other related diseases.

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