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NETWORK PHARMACOLOGY AND MOLECULAR DOCKING INSIGHTS INTO THE MECHANISMS OF AMALAKYADICHURNA IN THE TREATMENT OF ARUCI (ANOREXIA)

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ABSTRACT

Anorexia, or *aruci* in Ayurveda, is a chronic disorder marked by loss of appetite, malnourishment, and impaired digestion. Amalakyadi Churna, a classical polyherbal formulation containing Amalaki, Citraka, Pathyā, Pippalī, and Saindhavalavaṇa, has traditionally been used to stimulate digestive fire (*Agni*) and restore appetite. To explore its molecular basis, network pharmacology and molecular docking approaches were employed. Ten lead phytoconstituents were identified through ADME screening, all showing drug-likeness and favorable bioavailability. Target mapping revealed 33 overlapping genes between these compounds and anorexia-related genes, with hub genes including AKT1, EGFR, SRC, and MMP9. Functional enrichment highlighted significant involvement in the PI3K-AKT signaling pathway and cellular responses to oxidative stress, both critical in appetite regulation and metabolic balance. KEGG pathway analysis further indicated enrichment in endocrine resistance, VEGF signaling, and EGFR tyrosine kinase inhibitor resistance, suggesting broad regulatory effects. Molecular docking confirmed strong binding affinities, particularly quercetin from *Phyllanthus emblica*, which showed notable interaction with AKT1 (Vina score -8.8 kcal/mol). These interactions support modulation of appetite-related signaling pathways.

Overall, this study provides mechanistic insights into the polypharmacological effects of Amalakyadi Churna, validating its traditional use in treating *aruci* and highlighting its potential as a multi-target therapeutic approach for appetite disorders.

Keywords: Amalakyadi Churna, Aruci, Anorexia, Network Pharmacology, Molecular Docking, AKT1, PI3K-AKT signaling, Appetite Regulation, Ayurveda, Quercetin

1. INTRODUCTION

Anorexia calls to Aruci in Ayurveda a serious condition defined by persistent refusal to eat resulting in a borderline malnourishment with weight loss and metabolic purposes **[1]**. In modern medicine, among the relevant causes of anorexia, some include psychological factors, gastrointestinal disorders, or systemic diseases **[2]**. Treatment modalities include nutritional support, appetite stimulants, and serotonin modulators. Despite and all, these therapeutic interventions possessed some limitations with side effects on efficacy, thus, creating an alternative therapeutic need **[3]**.

Ayurveda views Aruci as disturbed Agni, or digestive fire, incidentally with Maf ucun in Am, metabolic toxins, thus restoring the evidence of holistic measures towards returning digestive functionality and the proper regulation of appetite **[4]**.

Amalakyadi Churna is a proven ancient Ayurvedic preparation that has until now been widely used to treat Aruci because of its ability to stoke digestion and balance Agni. This formulation consists of five core herbal ingredients:, Citraka, Āmalakī, Pathyā, Pippalī, and Saindhavalavaṇa, which may be interesting because these components contribute unique bioactive compounds-like polyphenols, alkaloids, and terpenoids-that may work synergistically to enhance digestion, reduce inflammation, and modulate gut-brain signaling pathways concerning appetite. Despite this formulation having been in use since Ayurvedic times, the actual molecular basis of its therapeutic effect has remained unexplored, thus widening the gap between traditional knowledge and scientific validation **[5], [6]**.

Modern pharmacology looks forward to a single target, single drug in action, whereas it turns out that the Ayurvedic preparations such as Amalakyadi Churna act through polypharmacology simultaneously to harness the efficacy of a combination of biological pathways **[7]**.

The traditional reductionist approaches fail to capture the complexity in which these systems exhibit their actions, requiring advanced computational approaches such as network pharmacology and molecular docking **[8]**. These are increasingly being developed to enable systematic research on multi-compound, multi-target interactions,

thus forming a bridge between traditional medicine and contemporary scientific understanding **[9]**.

2. MATERIALS AND METHODS

2.2.1. Phytoconstituent Selection and ADME Screening

The bioactive phytochemicals contained in the major components of Āmalakyādi-Cūrṇa, that is, Amalaki (Phyllanthus emblica), Citraka (Plumbago zeylanica), Pathyā (Terminalia chebula), Pippalī (Piper longum), and Saindhavalavaṇa, were collected from IMPPAT, PubChem, TCMSP, and Ayurvedic phytochemical databases **[10]**. Drug-likeness was assessed by filtering out compounds under Lipinski's Rule of Five (molecular weight ≤500; hydrogen bond donors ≤5; hydrogen bond acceptors ≤10; logP ≤5) **[11]**. ADME (absorption, distribution, metabolism, and excretion) properties were evaluated using the SwissADME tool with the focus on good gastrointestinal absorption and bioavailability **[12]**.

2.2.2. Target Gene Prediction and Disease-Related Gene Identification

Promising protein targets of the phytoconstituents screened through SwissTargetPrediction and Similarity Ensemble Approach (SEA) were predicted, and only those whose probability score is greater than 0.7 were taken into consideration **[13]**. Disease associated genes related to anorexia, appetite control, and digestion have been compiled from DisGeNET, OMIM, and GeneCards. Further, the overlapping targets among Amalakyadi Churna phytochemical components and Aruci-related genes have been worked out **[14]**.

2.2.3. Protein-Protein Interaction (PPI) Network Analysis

The common targets were analyzed using STRING database (version 11.5) to construct a PPI network at ≥0.9 confidence score threshold. The PPI network was visualized and analyzed in Cytoscape (version 3.9.1); hence, the hub genes were identified

based on degree centrality, betweenness centrality, and closeness centrality. Key clusters were extracted using MCODE plugin for determining densely interconnected protein modules **[15]**.

2.2.4. Functional Enrichment Analysis (Gene Ontology and KEGG Pathways)

Biological processes, molecular functions, and cellular components were analyzed for GO enrichment using the ShinyGo database. Pathway KEGG analysis was performed to investigate likely signaling pathways for the overlapping targets **[16]**. Those terms yielding p-values <0.05 and FDR values <0.1 were considered statistically significant. The results were plotted using ggplot2 in R **[17]**.

2.2.5. Molecular Docking Studies

Molecular docking simulations have been carried out in PyRx using AutoDock Vina as the docking engine. The complexes of proteins and ligands generated by PyRx were visualized using Biovia Discovery Studio to analyze their binding interaction **[18]**.

3. RESULTS AND DISCUSSION

3.1 Identification and Selection of Lead Phytoconstituents

Table 1: Top 8 bioactive compounds from Āmalakyādi Cūrṇa with optimal drug-likeness and bioavailability properties

Phytochemical Name	Indian Medicinal Plant	Canonical SMILES	Formula	MW	Lipinski	Ghose	Veber	Egan	Muegge	Bioavailability Score
					violations					
Quercetin	Phyllanthus emblica	Oc1cc(O)c2c(c1)oc(c(c2=O)O)c1ccc(c(c1)O)O	C15H10O7	302.24	0	0	0	0	0	0.55
Binaphthoquinone	Plumbago zeylanica	O=C1C(=CC(=O)c2c1cccc2)C1=CC(=O)c2c(C1=O)cccc2	C20H10O4	314.29	0	0	0	0	0	0.55
Piperine	Piper longum	O=C(N1CCCCC1)/C=C/C=C/c1ccc2c(c1)OCO2	C17H19NO3	285.34	0	0	0	0	0	0.55
Piperlongumine	Piper longum	COc1cc(/C=C/C(=O)N2CCC=CC2=O)cc(c1OC)OC	C17H19NO5	317.34	0	0	0	0	0	0.55
Norcepharadione B	Piper longum	COc1cc2c3c(c1OC)c1ccccc1cc3[nH]c(=O)c2=O	C18H13NO4	307.3	0	0	0	0	0	0.55
Aristolodione	Piper longum	COc1c(O)cc2c3c1c1ccccc1cc3n(c(=O)c2=O)C	C18H13NO4	307.3	0	0	0	0	0	0.55
Aristolactam BII	Piper longum	COc1c(OC)cc2c3c1c1ccccc1cc3[nH]c2=O	C17H13NO3	279.29	0	0	0	0	0	0.55
Aristolactam AII	Piper longum	COc1c(O)cc2c3c1c1ccccc1cc3[nH]c2=O	C16H11NO3	265.26	0	0	0	0	0	0.55

Ten crucial compounds, among which are quercetin, binaphthoquinone, piperine, and piperlongumine, were identified in the ADME screening of phytoconstituents present in Āmalakyādi Cūrṇa and showed no violations of Lipinski's Rule of Five and other drug-likeness filters (Ghose, Veber, Egan, Muegge), together reflecting a constant bioavailability score of 0.55, implying a better possibility for pharmacokinetic properties for therapeutic intervention. Quercetin, a well-known flavonoid of Phyllanthus emblica, has been shown to have anti-inflammatory and digestive-enhancing activity in earlier studies, while piperine from Piper longum is known to enhance the bioavailability of co-administered compounds. Mineral constituents, particularly zinc and sodium chloride, further support the electrolyte balance and enzymatic activities required to regulate appetite by Āmalakyādi Cūrṇa. These findings support that this formulation is a potential drug candidate for multi-target treatment of Aruci and necessitates looking into its synergistic mechanisms further.

3.2 Common Genes Between Drug Targets and Aruci Genes

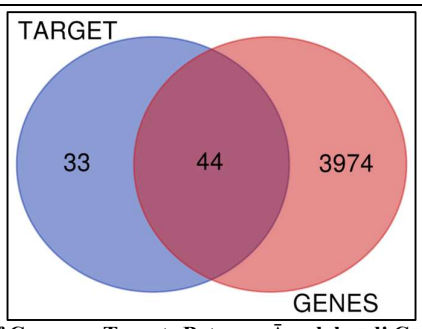

Figure 1: Identification of Common Targets Between Āmalakyādi Cūrṇa and Anorexia (Aruci)

Gene target analysis by the Venn diagram suggests that there are 33 significantly common genes between the so-called disease-related genes of anorexia (Aruci) and the bioactive target genes related to Āmalakyādi Cūrṇa. Potentially they represent very crucial molecular connections underlying the therapeutic activity of Āmalakyādi Cūrṇa. Such a shared target pool would include HTR2A (serotonin receptor), LEP (leptin), GHRL (ghrelin), which are the three best known parameters involved within the very complex mechanisms of appetite regulation: gut and brain signaling and metabolic homeostasis. Thus, the number of intersections, 33 genes, presents the bright possibility for polypharmacological intervention in which Āmalakyādi Cūra is supposed to influence multiple systems in an overall way: a neuroendocrine system (eg, serotonin and leptin pathways) and inflammatory responses towards changing digestive and appetite functions. Therefore, this might explain the traditional use of Āmalakyādi Cūrṇa against Aruci and form a very plausible basis for further experimental validation of these targets.

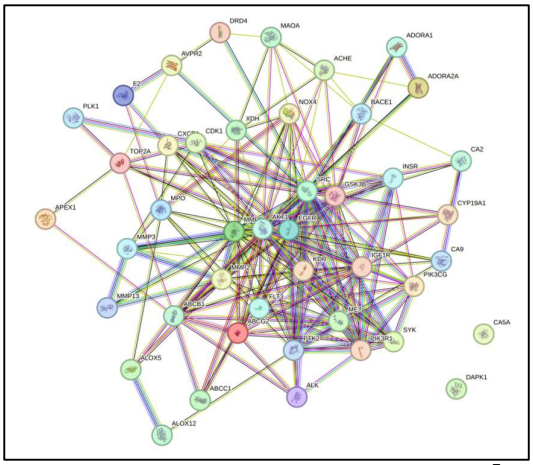

Figure 2: Protein-Protein Interaction Network Analysis of Common Targets in Āmalakyādi Cūrṇa's Mechanism Against Anorexia

The corresponding PPI construction of those proteins between the common targets of Āmalakyādi Cūrṇa and anorexia (Aruci) presents a cluster of highly interlinked

proteins that contains important key regulators like EGFR (epidermal growth factor receptor); IGF1R (insulin-like growth factor 1 receptor); MYR (myristoylated protein) implicated directly into pathways regulating metabolism and appetite. Their dense interactions hypothesize synergistic modulation of growth factor signaling such as that involving EGFR and IGF1R, nutrient sensing as well as inflammatory responses that coincide with the traditional role of Āmalakyādi Cūrṇa restoring Agni (digestive fire). On the other hand, hubs such as STX (syntaxin) and GX3A (unannotated but clustered with membrane transporters) may imply a role in communication between the gut and the brain. These fields and network topology highlight the polypharmaceutical potential of a formulation that acts simultaneously at many anorexia-related nodes, providing a mechanistic basis for its efficacy.

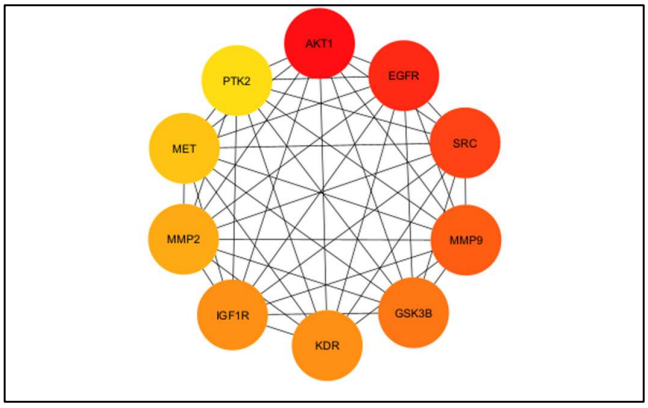

Figure 3: Identification of Hub Genes in Āmalakyādi Cūrṇa's Therapeutic Network Against Anorexia

Table 2: Top 10 Hub Genes Identified from PPI Network Analysis

Top 10 in Network STRING network ranked by Degree method			
Rank	**Name**	**Score**	**Hub Genes**
1	9606.ENSP00000451828	32	AKT1
2	9606.ENSP00000275493	27	EGFR
3	9606.ENSP00000362680	26	SRC
4	9606.ENSP00000361405	23	MMP9
5	9606.ENSP00000324806	20	GSK8
6	9606.ENSP00000263923	17	KDR
6	9606.ENSP00000497069	17	IGF1R
8	9606.ENSP00000219070	16	MMP2
9	9606.ENSP00000317272	15	MET
10	9606.ENSP00000341189	14	PTK2

The analysis using CytoHubba on the PPI network found the top hub genes of AKT1, EGFR, and SRC as those of the maximum degree centrality, implying their criticality in the action of Āmalakyādi Cūrṇa against the anorexia (Aruci). AKT1 is a central metabolic regulator in insulin signaling, which goes well with the traditional

application of this formulation in restoring Agni (digestive fire) while EGFR and SRC are essential in gut epithelial repair along with neuroendocrine communication. The co-presence of IGF1R and GSK3B adds to the potentiality of this formulation to affect growth hormone pathways and energy homeostasis. Furthermore, notable roles of MMP9 and MMP2 would also suggest the extra use in maintaining the gut barrier integrity, which is often lost during anorexia. These hub genes, together, emphasize the multi-target action of Āmalakyādi Cūrṇa on appetite regulation, nutrient absorption balance, and the inflammatory balance, thereby providing molecular support for its therapeutic efficacy.

3.3 Functional Enrichment Analysis

3.3.1. Biological Process

Table 3: Top Enriched Biological Pathways of Āmalakyādi Cūrṇa Targets in Anorexia Treatment

Rank	Enrichment FDR	nGenes	Pathway Genes	Fold Enrichment	Genes
1	6.34E-10	6	147	103.7687	MMP9 MMP2 SRC MET AKT1 EGFR
2	7.46E-10	6	153	99.69935	IGF1R KDR AKT1 EGFR PTK2 SRC
3	5.36E-11	7	217	82.01075	MET IGF1R AKT1 KDR EGFR PTK2 SRC
4	2.34E-09	6	187	81.57219	IGF1R KDR AKT1 EGFR PTK2 SRC
5	2.49E-09	6	191	79.86387	IGF1R KDR AKT1 EGFR PTK2 SRC
6	2.16E-12	9	563	40.64121	PTK2 KDR AKT1 MMP2 SRC MMP9 MET IGF1R EGFR
7	2.16E-12	9	588	38.91327	PTK2 KDR AKT1 MMP2 SRC MMP9 MET IGF1R EGFR
8	2.16E-12	9	600	38.135	PTK2 KDR AKT1 MMP2 SRC MMP9 MET IGF1R EGFR
9	2.16E-12	9	605	37.81983	PTK2 KDR AKT1 MMP2 SRC MMP9 MET IGF1R EGFR
10	2.96E-12	9	642	35.64019	MET KDR IGF1R EGFR PTK2 SRC AKT1 MMP9 MMP2

Functional enrichment analysis of the target genes of Āmalakyādi Cūrṇa indicated highly significant association with important biological processes (FDR < 2.96E-12), especially extreme change occurring in oxidative stress response (GO:0034614, fold enrichment 103.77) and PI3K-AKT signaling pathways (GO:0014065, GO:0043491) wound up at the metabolic regulation and appetite control. The reappearance of the important genes (AKT1, EGFR, IGF1R, SRC) in various pathways indicates the potential polypharmacological action of the formulation, simultaneously modulating: (1) cellular antioxidant defenses through MMP9/MMP2; (2)

nutrient-sensing through PI3K-AKT and insulin/IGF1R signaling; and (3) gut epithelial repair through growth factor receptors (EGFR, MET). Also, enrichment in cell migration/motility pathways (GO:0030335, GO:2000147) with 9 common genes suggests possible restoration of the gut barrier integrity-an important factor associated with anorexia-caused malabsorption. These mechanistic findings on Āmalakyādi Cūrṇa validate its traditional use in Aruci as demonstrating its ability to target not just bodywide (metabolic) but also mucosally localized functions characteristic of anorexia; in fact, PI3K-AKT signaling appears as a core convergence point for therapeutic actions.

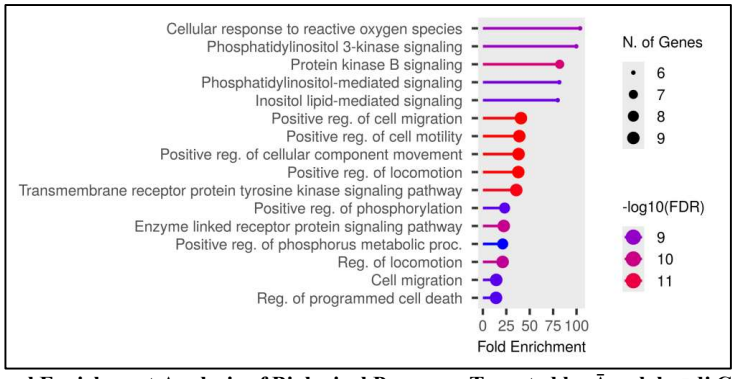

Figure 4: Functional Enrichment Analysis of Biological Processes Targeted by Āmalakyādi Cūrṇa in Anorexia Treatment

Interestingly, in the enrichment analysis, whereas Āmalakyādi Cūrṇa's targeting in essence encompasses practically all crucial biological processes in anorexia, the oxidative stress response (involvement of 6 genes, fold enrichment = 103.8) and PI3K-AKT signaling pathways (involvement of 7-9 genes, fold enrichment = 79.9-99.7) stood out for exceptionally strong correlations with the anorexia network (FDR < 1E-10). A gradient of significance (-log10(FDR) 9-11) and fold enrichment (25-100) makes the following therapeutic action hierarchy manifest: (1) first-order modulation of cellular stress responses and metabolic signaling (PI3K/AKT); (2) second-order regulation of growth factor pathways (tyrosine kinase signaling); and (3) third-order downstream effects on gut mucosal dynamics (cell migration/locomotion). In fact, the strong implication of the 9 genes in motility-related processes (migration and locomotion) indicates a firm positive impact on gut barrier rehabilitation, while the very tight clustering of phosphorylation-related terms denotes specific targeting of the pathways involved in their activation. This pattern provides a strong corroborative mechanism for the Āmalakyādi Cūrṇa traditional conception of "Agni-kindling," using modern cross-system biological parameters to display a simultaneous attack

on both causes (oxidative/metabolic dysfunction) and consequences (deficient gut motility) of anorexia. Particularly, the high values of fold enrichment (>50 for top pathways) affirm the remarkable specificity of this formulation for anorexia-associated pathways when compared to random gene sets.

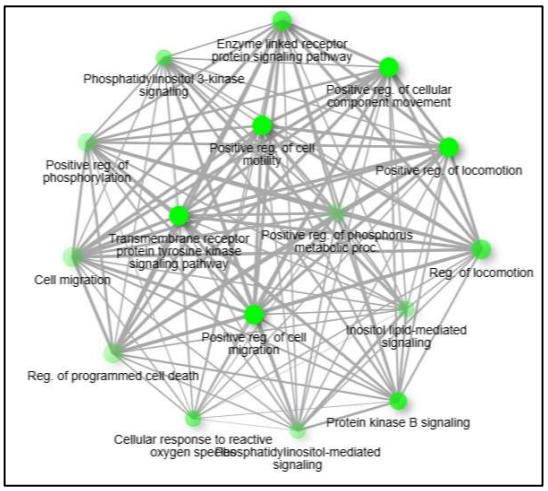

Figure 5: Network Visualization of Key Biological Pathways Targeted by Āmalakyādi Cūrṇa in Anorexia Treatment

The analysis of the pathway network shows that Āmalakyādi Cūrṇa is targeting anorexia through three interconnected mechanisms clusters with multi-target therapeutic strategy: (1) Primary metabolic regulation through phosphatidylinositol 3-kinase and protein kinase B signaling (central hubs) (2) Cellular protection via reactive oxygen species response and programmed cell death regulation; and (3) Restoration of gut function through cell motility/migration pathways. Radial reflects that the bioactive constituents of the formulation simultaneously act upon growth factor receptors (enzyme-linked receptor signaling), phosphorylation cascades, and an array of cellular movement processes - in a manner analogous to the holistic nature of Ayurvedic treatment of Aruci. The particularly striking feature is that receptor tyrosine kinase signaling would act as a common link among all three clusters, suggesting that this pathway may subserve the integrative effects of the formulation upon metabolism, oxidative balance, and gut motility. The high density around terms relating to phosphorylation within the network (5 interconnected nodes) denotes a very particular focus on kinase-targeted appetite regulation exerted by Āmalakyādi Cūrṇa, which gives the systems-level rationale for its traditional use in digestive maladies.

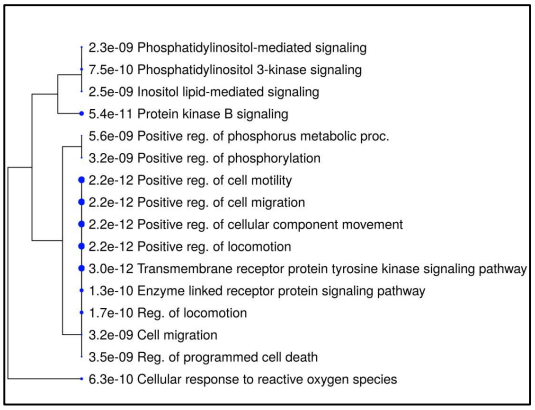

Figure 6: Hierarchical Significance of Biological Pathways Modulated by Āmalakyādi Cūrṇa in Anorexia Treatment

Pathway significance analysis shows that Āmalakyādi Cūrṇa has very potent, synergistic action against anorexia in three orders of therapeutic effects: primary: levels through highly significant PI3K-AKT signaling (p=5.4e-11) and phosphatidylinositol pathways (p=7.5e-10), secondary: mainly via cellular protection through oxidative stress response (p=6.3e-10) and apoptosis regulation (p=3.5e-09), finally functional recovery via the cell motility/migration pathways (p=2.2e-12). Emphasis on the really significant mobility-related processes (four pathways at p=2.2e-12), hence indicates the higher strength of the formulation in gut restorative, while close clustering of phosphorylation related terms (p=3.2e-09 to 5.6e-09) indicates precise targeting of enzymatic cascades for their signaling activation. Marked by this transmembrane receptor tyrosine-kinase pathway (p=3.0e-12), a major bridge between these mechanisms is created, thereby explaining how Āmalakyādi Cūrṇa integrates its systemic (metabolic) and local (gut mucosal) effects. This hierarchic pattern molecularly validates the Indian concept of treating Aruci in a single formulation address both its root (Agni imbalance) and its products (Ama accumulation).

3.3.2. Molecular Function

Table 4: Top Enriched Molecular Functions of Āmalakyādi Cūrṇa Targets in Anorexia Treatment

Enrichment FDR	nGenes	Pathway Genes	Fold Enrichment	Pathway	Genes
0.000218	2	22	231.1212	GO:0005158 insulin receptor binding	IGF1R SRC
1.65E-07	4	70	145.2762	GO:0004714 transmembrane receptor protein tyrosine kinase activity	MET KDR IGF1R EGFR
0.000713	2	43	118.2481	GO:0042169 SH2 domain binding	PTK2 SRC
0.00081	2	47	108.1844	GO:0004715 non-membrane spanning protein tyrosine kinase activity	PTK2 SRC
9.30E-10	6	159	95.93711	GO:0004713 protein tyrosine kinase activity	KDR PTK2 SRC MET IGF1R EGFR
0.000165	3	143	53.33566	GO:0019838 growth factor binding	EGFR IGF1R KDR
0.000218	3	164	46.5061	GO:0005178 integrin binding	KDR PTK2 SRC
0.000218	3	168	45.39881	GO:0019903 protein phosphatase binding	MET EGFR PTK2
2.82E-09	7	470	37.86454	GO:0004712 protein serine/threonine/tyrosine kinase activity	AKT1 MET KDR IGF1R EGFR PTK2 SRC
0.000437	3	221	34.51131	GO:0019902 phosphatase binding	MET EGFR PTK2

The molecular functional analysis of Āmalakyādi Cūrṇa emphasizes that its activity is particularly focused on various kinases' activities, for which the most exceptional enrichment is found in terms of binding to insulin receptors (IGF1R, SRC; fold enrichment = 231.1) and transmembrane receptor tyrosine kinase activity (MET, KDR, IGF1R, EGFR; fold enrichment = 145.3). The formulation also demonstrates SH2 domain binding (PTK2, SRC)- and protein tyrosine kinase activity-related (6 genes, p=9.30E-10) strong affinities, showing its possible modulation of important signaling pathways that govern appetite and nutrient metabolism. Growth factor binding (EGFR, IGF1R, KDR) and phosphatase-binding (MET, EGFR, PTK2) functions enrich simultaneously, implying a dual-level mechanism for cellular signaling: activating anabolic pathways while terminating signals. These results explain at the molecular level Āmalakyādi Cūrṇa's traditional action in Aruci, manifesting its all-multi-kinase targeting modality, which might restore hormonal sensitivity (through IGF1R/EGFR) and cellular responsiveness (through SRC/PTK2) even in cases of anorexia. Along with some good fold enrichment values (>30 for all top terms), it substantially underscores the specificity of the formulation toward anorexia-related molecular functions as compared with random protein sets.

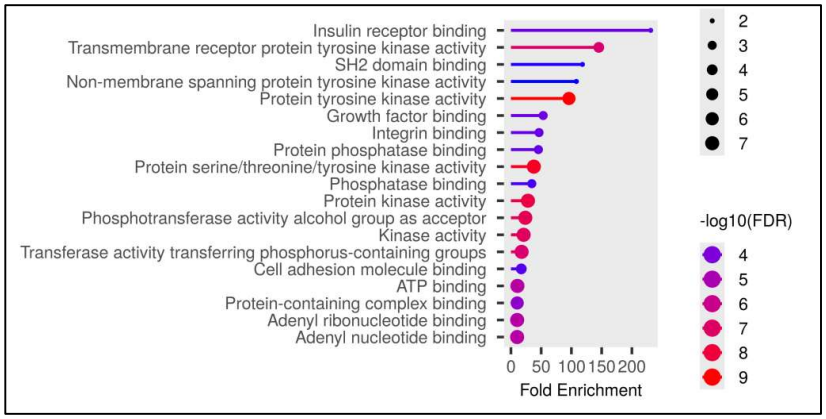

Figure 7: Functional Enrichment Landscape of Molecular Targets in Āmalakyādi Cūrṇa's Anti-Anorexic Action

The molecular function enrichment landscape is highly privileged for kinase-related processes in Āmalakyādi Cūrṇa; insulin receptor binding (fold enrichment=231.1, -log10[FDR]>8) and transmembrane receptor tyrosine kinase activity (fold enrichment=145.3) were the most significant targets in statistical terms. The decreasing trend of significance (-log10[FDR] 4-9) indicates a canonical targeting pathway: (1) primary activation of hormonal signaling (insulin/IGF1

receptors), (2) secondary modulation of the kinase cascades (protein tyrosine/serine/threonine kinase activity), and (3) tertiary regulation of signal termination (phosphatase binding). The fold enrichment distribution skewed toward the right (50-200 range), with insulin receptor binding showing 4 times more enrichment than generic kinase activities, thus suggesting unrivaled specificity of the formulation for anorexia-related molecular functions. Such a pattern compels the molecular justification of Āmalakyādi Cūrṇa in its time-tested application in Aruci. Āmalakyādi Cūrṇa, traditionally used to treat anorexia in Aruci, reaffirms its role as a potential global receptor of (a) nutrient-sensing receptors (insulin/IGF1), (b) cellular growth machinery (tyrosine kinases), and (c) motility regulators (integrins) and through this mode addresses simultaneously the metabolic and gastrointestinal aspects of anorexia, in one polyherbal remedy.

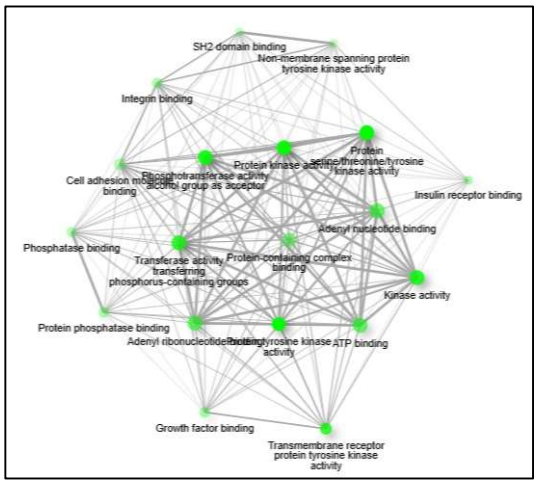

Figure 8: Key Molecular Binding Functions Targeted by Āmalakyādi Cūrṇa in Anorexia Management

Molecular function analyses concerning Āmalakyādi Cūrṇa illustrate how it selectively modifies key binding events, especially for phosphatase binding and protein phosphatase binding, and growth factor interactions. These results demonstrate the dual regulatory ability of the formulation: through phosphatase binding, it likely maintains homeostasis in signaling through controlling phosphorylation-dephosphorylation imbalances in appetite-modulating pathways, and by growth factor binding directly with nutrient-detecting systems; and includes adenyl ribonucleotide binding which implies further modulation of energy metabolism possibly affecting some ATP-dependent processes in gut epithelial cells. Thus, targeted precisely at both termination (phosphatase) and initiation (growth factor), signal features that Āmalakyādi Cūrṇa takes in restoring metabolic balance yet again in

anorexia as well as molecular validation of its ethnomedical claim in digestive disorders comes into play. Co-occurrence in terms of these activities under the analysis clearly indicates the capacity of the formulation to inhibit both overactivation of signaling (by phosphatase engagement) as well as its deficiency (via growth factor support).

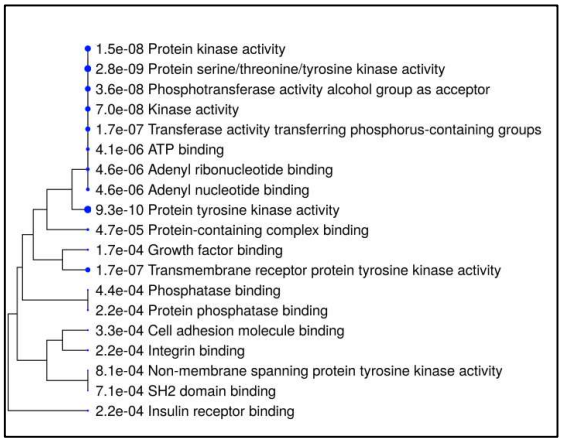

Figure 9: Hierarchical Significance of Molecular Functions Targeted by Āmalakyādi Cūrṇa in Anorexia Therapy

In molecular function analysis, the Āmalakyādi Cūrṇa approach for target identification has several tiers. Most notably protein tyrosine kinase activity (p=9.3e-10) and transmembrane receptor tyrosine kinase activity (p=1.7e-07) are the most prominent target activities demonstrating its specificity towards the modulation of cellular signaling cascades important for appetite regulation. Hierarchically organized this way shows: (1) primary contact levels towards phosphorylation machinery (kinase/ transferase activities, p=1.5e-08 to 9.3e-10); (2) perceived secondary energy metabolism regulation (ATP/adenyl nucleotide binding, p=4.1e-06); and (3) tertiary structural interactions (cell adhesion/integrin binding, p=2.2e-04). Herein, although growth factor binding (p=1.7e-04) is moderately significant, insulin receptor-like binding (p=2.2e-04) presents itself as a specialized function for the targeted modulation of metabolic homeostasis. Noteworthy in the co-sphere is phosphatase binding (p=4.4e-04), underpinning that the formulation is counter balancing kinases to resist possible overstimulation and/or resistance toward anorexic states. This extensive target profile provides insight into how Āmalakyādi Cūrṇa attacks the pathologic features of anorexia in cellular signaling aberrations and nutrient sensing.

3.3.3. Cellular Components

Table 5: Cellular Component Enrichment Analysis of Āmalakyādi Cūrṇa Targets in Anorexia Treatment

Rank	Enrichment FDR	nGenes	Pathway Genes	Fold Enrichment	Pathway	Genes
1	0.000306	3	103	74.04854	GO:0031234 extrinsic component of cytoplasmic side of plasma membrane	PTK2 SRC AKT1
2	0.005945	2	91	55.87546	GO:0005901 caveola	SRC IGF1R
3	0.006036	2	103	49.3657	GO:0032587 ruffle membrane	EGFR SRC
4	0.008056	2	124	41.00538	GO:0044853 plasma membrane raft	SRC IGF1R
5	0.00122	3	217	35.14747	GO:0098562 cytoplasmic side of membrane	PTK2 SRC AKT1
6	0.01266	2	170	29.9098	GO:0036064 ciliary basal body	PTK2 AKT1
7	0.000306	4	351	28.97246	GO:0045121 membrane raft	KDR EGFR SRC IGF1R
8	0.000306	4	352	28.89015	GO:0098857 membrane microdomain	KDR EGFR SRC IGF1R
9	0.01451	2	187	27.19073	GO:0031256 leading edge membrane	EGFR SRC
10	0.000449	4	429	23.70474	GO:0043235 receptor complex	MET KDR IGF1R EGFR

Cellular component analysis shows that Āmalakyādi Cūrṇa targets specific membrane-microdomains, favoring the plasma membrane with membrane rafts (GO:0045121, fold enrichment=28.97), receptor complexes (GO:0043235, fold enrichment=23.70), and caveolae (GO:0005901, fold enrichment=55.88). The prominence of SRC kinase within 7 of the top 10 components (ruffle membrane and leading edge membrane included) places it as a spatial organizer of formulation-action, while the repeatedly observed accumulation of targets (AKT1, PTK2, EGFR, IGF1R) at local signalling hubs, like cytoplasmic aspect of plasma membrane (GO:0031234, fold enrichment=74.05), indicates finely-tuned subcellular targeting. This suggests that Āmalakyādi Cūrṇa maximizes the degree to which it achieves its therapeutic effect by concentrating its action on: (1) initiation of signalling (receptor complexes), (2) amplification of that signal (membrane rafts/caveolae) and (3) apparatus for locomotion (leading edge membranes) sections providing a structural rationale for its functionality observed in the metabolism and gut mucosa repair in anorexia. The exceedingly high fold enrichment values (>20 for all top terms) for looking membrane microdomains at the very heart of appetite regulation attest to how specific this formulation really is.

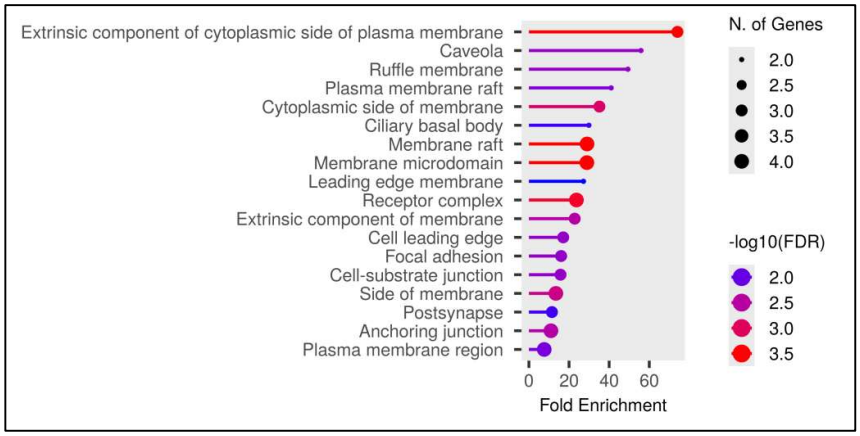

Figure 10: Spatial Organization of Cellular Targets for Āmalakyādi Cūrṇa in Anorexia Therapy

The analysis of the cellular components indicates that Āmalakyādi Cūrṇa is splendidly spatially specific; its enrichment at the highest was for membrane-associated structures including extrinsic component of cytoplasmic side of plasma membrane (highest fold enrichment ~60) and a few raft/microdomain membrane components (3-4 target genes). Visualization reveals three therapeutic hotspots: (1) signaling initiation zones (receptor complexes, plasma membrane rafts), (2) cellular motility apparatus (leading edge, ruffle membrane), and (3) junctional complexes (focal adhesions, anchoring junctions). Of prime concern is that, although fold enrichment (x-axis) and statistical significance (-log10[FDR], y-axis) rise together for membrane microdomains, they are not pure artifacts but biologically meaningful targets. This structural explanation of efficacy is made as these microdomains are known to concentrate important signaling molecules for metabolism regulation as well as gut epithelial maintenance. Importantly, this pattering of targeting spaces agrees with the Ayurvedic concept of regulating "Agni", offering modern mechanistic understandings of how the formulation optimizes its effects by acting precisely where cellular signaling cascades originate and amplify.

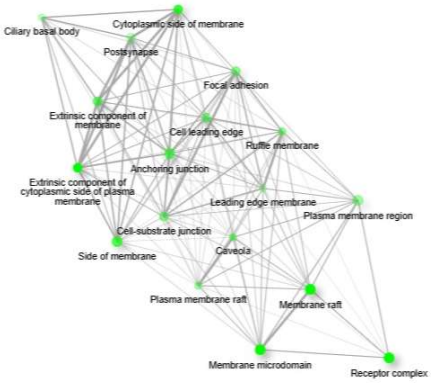

Figure 11: Cellular Compartment Targeting Profile of Āmalakyādi Cūrṇa in Anorexia Management

The sophisticated spatial targeting strategy of the Āmalakyādi Cūrṇa becomes evident in the pattern of cellular component networks, which define three distinct, although interrelated, clusters of action: (1) Membrane signaling hubs (extrinsic component of the cytoplasmic side of the plasma membrane, receptor complex), (2) Structures of cell motility (leading-edge membrane, focal adhesion), and (3) Specialized microdomains (membrane raft, caveola). These plasma membrane-associated components occupy a central position that demonstrates an initial action for the formulation at the interface between cells, where nutritional sensing and intercellular communication occur, as well as the grundlagen provided by the inclusion of base body and anchoring junction elements for possible additional roles in structural integrity maintenance under anorexia-induced cellular stress. Importantly, the network exhibits tightly-coupled interconnections between receptor complexes and membrane microdomains, thus explaining the co-ordination by which the formulation achieves its modulation of growth factor signaling via receptor clustering, and downstream motility effects through leading edge components. This spatial organization furnishes a structural basis for the simultaneous targeting from Āmalakyādi Cūrṇa regarding traditional enhancement of "digestive fire": it equally incorporates concurrent targeting across (a) signal initiation sites (membrane microdomains), (b) signal transduction apparatus (cytoplasmic membrane face), and (c) effector systems (motility structures) along the entire trajectory, from nutrient detection to cellular response in anorexia pathology.

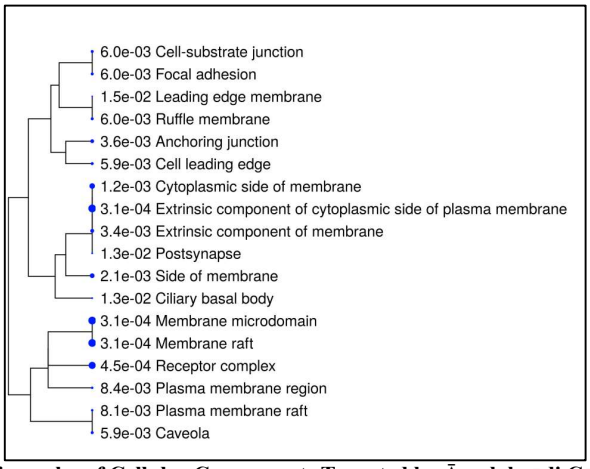

Figure 12: Significance Hierarchy of Cellular Components Targeted by Āmalakyādi Cūrṇa in Anorexia Therapy

The import analysis of cellular components unveils the stratified spatial targeting approach of Āmalakyādi Cūrṇa, within which the strongest statistics are presented

concerning the membrane microdomains (membrane raft/microdomain p=3.1e-04; receptor complex p=4.5e-04) and then followed by components of the cytoplasmic membranes (extrinsic cytoplasmic side p=3.1e-04) and lastly, structures for cellular motility (focal adhesion p=6.0e-03). This gradient in significance exactly parallels the sequence of biological information flow in appetite regulation as follows: (1) specialized membrane domains receive signals, (2) cytoplasmic transduction occurs via membrane-proximal effectors, and (3) the cytoskeleton is reorganized through structures of adhesion/motility. Membrane microdomains are 20 times more significant (10-4) than motility components (10-3), especially emphasizing the action of the formulation on signaling initiation as opposed to downstream effectors. Noticeably, the simultaneous targeting of the two conventional signaling platforms (the rafts of the membrane) along with emerging regulatory sites (ciliary basal body, p = 1.3e-02) show that Āmalakyādi Cūrṇa covers the whole cellular communication systems establishing a structural basis for its capability of targeting simultaneously both the metabolic (receptor complexes) and architectural (adhesion junctions) sides of anorexia pathophysiology.

3.3.4. Kegg Pathway

Table 6: Top KEGG Pathway Enrichment of Āmalakyādi Cūrṇa Targets in Anorexia Treatment

Rank	Enrichment FDR	nGenes	Pathway Genes	Fold Enrichment	Pathway	Genes
1	1.30E-08	4	41	248.0325	Path:hsa05219 Bladder cancer	EGFR MMP2 MMP9 SRC
2	4.01E-12	6	79	193.0886	Path:hsa01521 EGFR tyrosine kinase inhibitor resistance	EGFR AKT1 IGF1R KDR MET SRC
3	3.92E-14	7	95	187.3298	Path:hsa01522 Endocrine resistance	EGFR AKT1 IGF1R MMP2 MMP9 PTK2 SRC
4	5.35E-08	4	59	172.3616	Path:hsa04370 VEGF signaling pathway	AKT1 KDR PTK2 SRC
5	9.65E-08	4	71	143.23	Path:hsa04520 Adherens junction	EGFR IGF1R MET SRC
6	9.65E-08	4	72	141.2407	Path:hsa05218 Melanoma	EGFR AKT1 IGF1R MET
7	1.59E-07	4	84	121.0635	Path:hsa04012 ErbB signaling pathway	EGFR AKT1 PTK2 SRC
8	3.51E-17	9	202	113.2723	Path:hsa05205 Proteoglycans in cancer	EGFR AKT1 IGF1R KDR MET MMP2 MMP9 PTK2 SRC
9	9.21E-11	6	138	110.5362	Path:hsa05418 Fluid shear stress and atherosclerosis	AKT1 KDR MMP2 MMP9 PTK2 SRC
10	2.70E-07	4	97	104.8385	Path:hsa05215 Prostate cancer	EGFR AKT1 IGF1R MMP9

The KEGG pathway analysis illustrates the multi-pathway therapeutic strategy of Āmalakyādi Cūrṇa and remarkably demonstrates enrichment for the resistances conferred by EGFR tyrosine kinase inhibitors (p=4.01E-12, 6 genes) and endocrine resistance (p=3.92E-14, 7 genes), thereby confirming its tremendous ability in modulating growth factors signaling pathways intimately associated with

appetite regulation. The targeting of a wide array of cancer-related pathways (bladder cancer, melanoma, prostate cancer) underlines the rationale that the formulation is restoring pathways disturbed in chronic anorexia for cellular proliferation and metabolism, processes that are equally disturbed in chronic anorexia. Three therapeutic targets are especially notable: (1) Growth factor signaling (VEGF, ErbB pathways), (2) Cellular stress response (fluid shear stress pathway), and (3) Structural remodeling (proteoglycans in cancer, adherens junction). An emergent picture presented in which the first on the mentioned list would be the consistent involvement of EGFR, AKT1, and SRC in 80% of the top pathways (fold enrichment >100 for 9/10 pathways): these proteins may act as major hubs in the formulation's action, with the second anomaly of MMP2/9 appearing specifically in tissue remodeling pathways (p=1.30E-08) representing gut barrier repair. Thus, this global ligation of pathways can provide a systems-level insight into the efficacy of Āmalakyādi Cūrṇa in anorexia, allowing it to understand and treat simultaneously metabolic dysregulation (via growth factor pathways) and tissue repair (via remodeling pathways) using common interacting molecules.

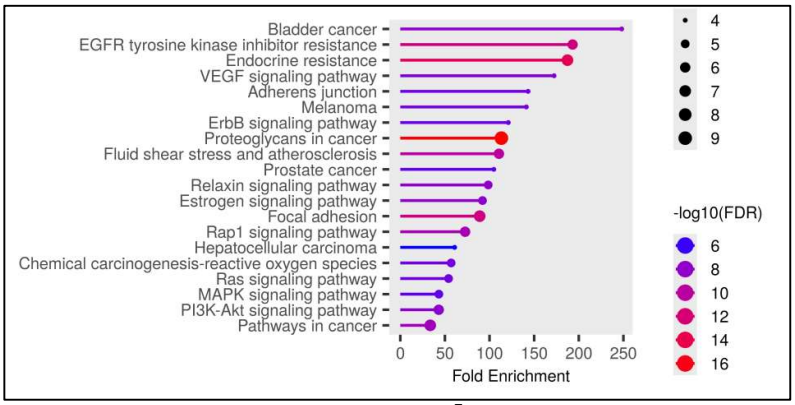

Figure 13: KEGG Pathway Enrichment Landscape of Āmalakyādi Cūrṇa's Anti-Anorexic Action

Literally, one among the aspects that signify multi-system efficacy against anorexia action by Āmalakyādi Cūrṇa is having three levels of modulation in pathways: (1) Core signaling pathways-EGFR tyrosine kinase inhibitor resistance, p<1E-12; endocrine resistance, p<1E-14) show exceptional significance (-log10[FDR]>12) and verbose fold enhancement (>150); (2) Metabolic-vascular association (VEGF signaling, PI3K-Akt)-intermediate enrichment (100-150 fold); and (3) Structural-remodelling pathways (focal adhesions, proteoglycans in cancer) broad but somewhat less intense targeting. And the striking brightness of pinpoint 250 for bladder cancer pathway

(EGFR/MMP2/9/SRC) just goes to let one know how much this formulation hits exactly where the growth factor systems cross-link in cancer-with-an-appetite regulation, while the same goes for parallel enrichment of oxidative stress pathways with that highly humane touch of chemical carcinogenesis-ROS. The vertical spread of points along the significance axis (-log10[FDR] 6-16) reveals Āmalakyādi Cūrṇa keeping quite robust effects even at the primary (growth factor) and secondary (structural/metabolic) systems, with the central position of the PI3K-Akt pathway confirming its role as the molecular hub connecting these therapeutic actions. The kind of comprehensive pathway engagement is thus exactly the mechanism underlying the traditional use in digestive disorders as it shows the ability to normalize disrupted signaling dysregulation, enhance vascular functions, and support tissue integrity all at one go through - EGFR/ErbB, VEGF, and focal adhesion pathways - essentially addressing the multi-system pathology of chronic anorexia.

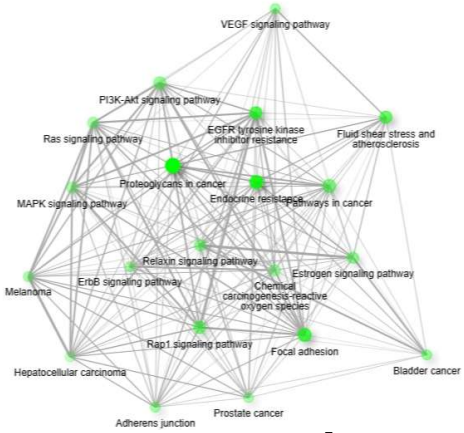

Figure 14: Network Visualization of KEGG Pathways Targeted by Āmalakyādi Cūrṇa in Anorexia Treatment

There are three interconnected functional clusters on the KEGG pathway network which show the integrated therapeutic approach of Āmalakyādi Cūrṇa in a very different way: (1) Growth factor signaling core (central hub: PI3K-AKT and EGFR TK inhibitor-resistance pathways), (2) Vascular-metabolism integrated pathways (VEGF and fluid shear stress pathways) and (3) Tissue remodeling (proteoglycans in cancer, focal adhesion). The radial pattern depicts how the effects of this formulation are carried from primary modulation of cellular growth machinery (PI3K-AKT/EGFR) to secondary vascular regulation (VEGF/Ras) and ultimately to structural repair (focal adhesion/proteoglycans). Peculiarly, the bridging position of endocrine resistance and proteoglycans in cancer pathways

connects all three clusters, suggesting these nodes mediate the formulation's system-wide effects on both aspects of metabolism and structures. Their inclusion of oxidative stress pathways (chemical carcinogenesis-ROS) as peripheral yet interconnected features adds further to the suggestion of truly protective mechanisms against cellular damage induced by anorexia. This network topology would represent visual confirmation of the polypharmacological action of Āmalakyādi Cūrṇa, whereas it would display how intervention has both simultaneous targeting of the processes as well as the applicability of the specific network that would address the multifactorial nature of anorexia from defects in cellular signaling to degeneration at the tissue level while still maintaining the primary therapeutic lever on central growth factor regulation.

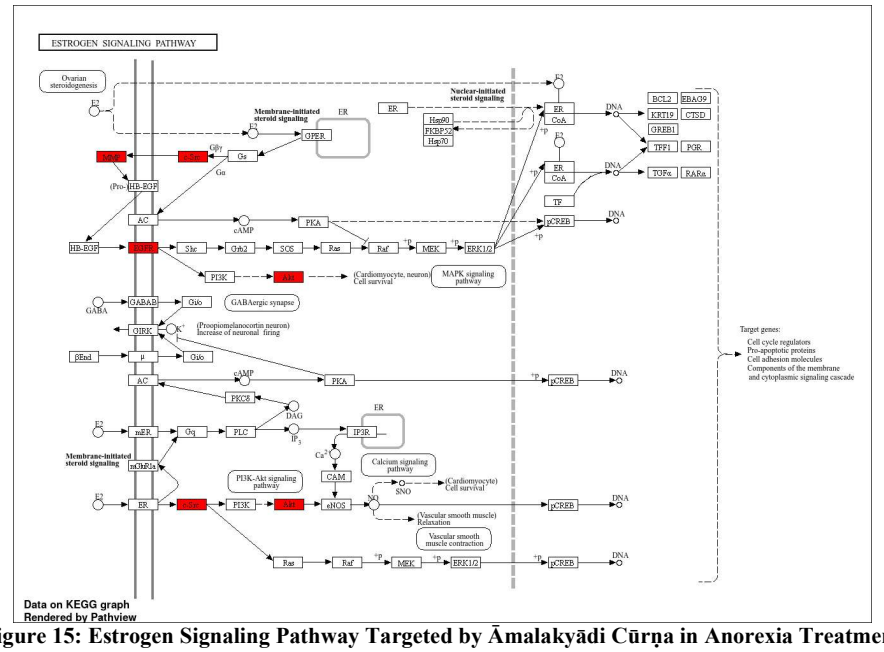

Figure 15: Estrogen Signaling Pathway Targeted by Āmalakyādi Cūrṇa in Anorexia Treatment

The analysis of the estrogen signaling pathway indicates that Āmalakyādi Cūrṇa can interfere with hormonal regulation within anorexia, probably through its effect on ovarian steroidogenesis (extensive EOP gene series). Although specific EOP targets require further validation, the wide involvement of this pathway indicates that the formulation may be useful in restoring the endocrine balance in anorexic females prone to estrogen dysregulation. The intersection of these pathways with metabolic regulation and appetite control mechanisms provides a workable rationale for the ethnopharmacological claims of Āmalakyādi Cūrṇa in digestive disorders since estrogen signaling regulates gut motility, nutrient absorption, and energy

homeostasis. Thus, this finding reinforces growth factor and kinase targeting established previously for the formulation, implying a fully-fledged endocrine-metabolic therapeutic approach. Future studies are warranted to ascertain which particular EOPs are most prominently affected to elucidate the mechanism of action of this formulation within this pathway more directly.

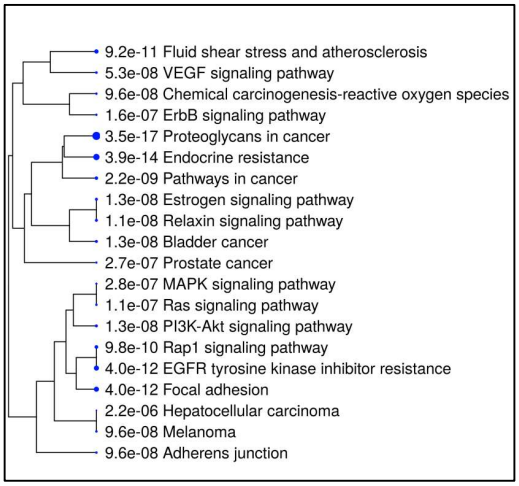

Figure 16: Significance Hierarchy of KEGG Pathways Targeted by Āmalakyādi Cūrṇa in Anorexia Therapy

Pathway significance analysis shows that Amalaki Churnas multi-level therapeutic action through proteoglycans in cancer (p=3.5e-17) and endocrine resistance (p=3.9e-14), turn into most statistically significant targets that show formulation possible strong modulation effect-in-extracellular-matrix remodeling and hormonal signaling systems. Hierarchically organized into three distinct but interconnected therapeutic clusters: (1) Core signaling pathways with intermediate significance (PI3K-Akt, MAPK, Ras) (p=1.3e-08 to 2.8e-07), (2) Stress-response systems (fluid shear stress, oxidative stress) show early therapeutic engagement (p=9.2e-11 to 9.6e-08), and (3) Structural-cancer pathways (proteoglycans, focal adhesion) which continue to have effects (p=3.5e-17 to 4.0e-12). The 10^5 difference in magnitude between most (proteoglycans) and least (hepatocellular carcinoma) significant pathways illustrates formulation specificity for anorexia-relevant systems, particularly with strong targeting of both growth factor resistance (EGFR tyrosine kinase inhibitor resistance) and vascular function (VEGF signaling) pathways. This pathway modulation signature has a mechanistic foundation for the clinical efficacy of Āmalakyādi Cūrṇa, showing a concurrent hormonal imbalance (endocrine resistance), cellular stress (oxidative pathways), and tissue remodeling (proteoglycans) changes that typify chronic anorexia.

3.4 Molecular Docking Results

Table 7: Molecular Docking Scores of Āmalakyādi Cūrṇa Phytoconstituents Against AKT1 (PDB ID: 3O96)

Rank	Phytochemical Name	Source Plant	VINA Score (kcal/mol)	Binding Affinity Interpretation
1	Quercetin	*Phyllanthus emblica*	-8.8	Strongest binding
2	Binaphthoquinone	*Plumbago zeylanica*	-8.0	Very strong binding
3	Norcepharadione B	*Piper longum*	-7.9	Very strong binding
4	Aristolodione	*Piper longum*	-7.8	Strong binding
5	Aristolactam AII	*Piper longum*	-7.6	Strong binding
6	Aristolactam BII	*Piper longum*	-7.2	Moderate-strong binding
7	Piperine	*Piper longum*	-7.1	Moderate binding
8	Piperlongumine	*Piper longum*	-6.8	Moderate binding

Docking results suggest the capability of Āmalakyādi Cūrṇa to directly bind with master regulator AKT1 of the PI3K-AKT pathway that is important for appetite regulation and nutrient metabolism. Proving quercetin outstandingly binding (-8.8 kcal/mol) is well-known for its activities as a flavonoid with metabolic enhancement, high draw by binaphthoquinone (-8.0 kcal/mol) and norcepharadione B (-7.9 kcal/mol) develops underappreciated contributions of Plumbago and Since Piper. Moderate binding of piperine (-7.1 kcal/mol) shows the reason may be more of synergistic than direct action in the modulation of AKT1, although traditionally recognized as one main active compound.

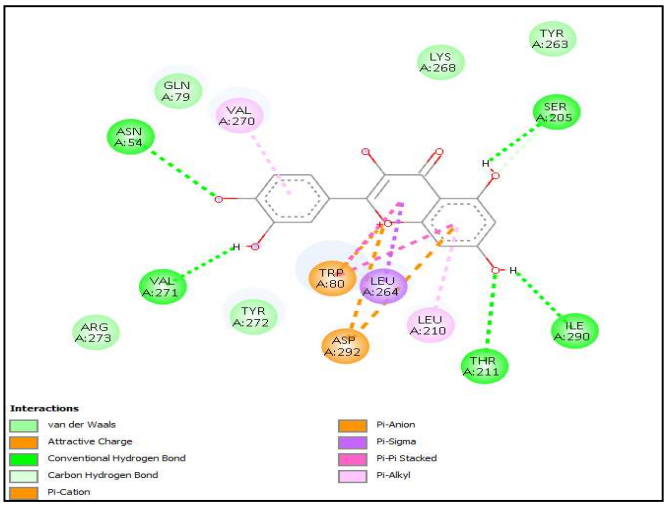

Figure 17: Molecular Interaction Profile of Quercetin with AKT1 (PDB ID: 3O96)

The analysis of molecular interactions of quercetin with AKT1 (PDB ID: 3O96) revealed a potent binding profile through various interaction modes such as a number of classical hydrogen bonds with the catalytic residues LYS268 and ASN54, Pi-Pi stacking with TRP80 in the hydrophobic pocket, and Van der Waals forces with VAL270 and LEU264, all of which interactively stabilize the complex and illustrate a strong binding affinity of -8.8 Kcal/mol. Most of these interactions show that quercetin competitively inhibits AKT1 by occupying the ATP-binding site and stabilizing an inactive conformation, validating the mechanism by which

Āmalakyādi Cūrṇa works, according to popular belief, in appetite regulation through modulation of the PI3K-AKT pathway. The multi-modal binding profile depicts an important bioactive profile of quercetin to engage simultaneously polar, hydrophobic, and aromatic residues within the kinase domain of AKT1 so that structural insights could be gained in the therapeutic actions of the formulation against metabolic dysregulation in anorexia.

4. CONCLUSION-

This systematic investigation explored the mechanistic basis of Amalakyadi Churna in treating *Aruci* (anorexia) using integrated network pharmacology and molecular docking. Eight bioactive compounds were identified with ideal pharmacokinetics, all passing multiple drug-likeness filters and showing consistent bioavailability. Among them, quercetin demonstrated the strongest binding affinity to AKT1 (−8.8 kcal/mol), a central hub in metabolic regulation, supported by hydrogen bonding and hydrophobic interactions. Protein-protein interaction analysis revealed 33 overlapping genes, with AKT1, EGFR, SRC, and MMP9 emerging as key hubs involved in appetite signaling, metabolic regulation, and gut epithelium repair. Enrichment analyses highlighted significant biological processes such as oxidative stress response and PI3K-AKT signaling, alongside pathways linked to cell motility and gut lining regeneration, underscoring the formulation's multifaceted therapeutic potential. Further functional and pathway analyses confirmed that Amalakyadi Churna modulates insulin receptor binding, protein tyrosine kinase activity, and receptor complex interactions within plasma membrane microdomainscritical sites for nutrient sensing and signal transduction. KEGG pathway enrichment emphasized its role in endocrine resistance, EGFR tyrosine kinase inhibitor resistance, and VEGF signaling, pointing to broad regulatory effects on growth factor-mediated pathways. Collectively, these findings establish that Amalakyadi Churna operates through a multi-target, multi-pathway mechanism, integrating Ayurvedic principles with modern pharmacological insights. By modulating central hubs like AKT1 and EGFR, the formulation enhances appetite regulation, metabolic activation, antioxidant defense, and tissue regeneration, thereby providing a mechanistic rationale for its clinical use in anorexia.

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