Revisiting Itrifal-e-Aftimoon: A Unani Polyherbal Formulation for Cancer Management and Research

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Abstract

Cancer remains a major global health challenge, with conventional therapies limited by toxicity, drug resistance, and accessibility issues. Itrifal Aftimoon, a classical Unani polyherbal formulation from the National Formulary of Unani Medicine, contains twelve botanical and mineral ingredients including Triphala (Terminalia chebula, Emblica officinalis, Terminalia belerica), Plumbago zeylanica, Cuscuta reflexa, and Cassia angustifolia. These herbs provide diverse phytochemicals gallic acid, ellagic acid, plumbagin, flavonoids, and polyphenols enabling multi-targeted anticancer mechanisms.Gupta et al. (2022) demonstrated that Itrifal-e-Aftimoon potentiates imatinib's anti-leukemic effects in chronic myeloid leukemia by modulating FAK/STAT/Akt/ERK signaling pathways. The formulation exhibits antioxidant activity via Nrf2-ARE activation, anti-inflammatory effects through NF-κB and COX-2 suppression, immunomodulation enhancing natural killer cells, and selective cytotoxicity against cancer cells while sparing normal cells. Preclinical studies show tumor growth inhibition and improved survival in animal models. Clinical observations suggest enhanced quality of life and reduced chemotherapy toxicities, though rigorous trials are limited. Toxicological studies indicate favourable safety profiles with high therapeutic margins, though drug interactions require monitoring. Future research priorities include randomized controlled trials, pharmacokinetic studies, standardization protocols, bioactive compound identification, and nanoformulation development for improved bioavailability. Integrating traditional Unani knowledge with modern pharmaceutical sciences offers opportunities for evidence-based cancer therapeutics that address current oncological challenges while providing safer, accessible treatment options globally.

Keywords: Cancer, Unani , Itrifal aftimoon, immunomodulation, Oxidative stress, Antioxidant

Introduction

Cancer remains one of the most formidable health challenges globally, characterized by uncontrolled cellular proliferation and metastatic potential. Despite significant advances in conventional oncology, including chemotherapy, radiotherapy, and targeted therapies, challenges persist regarding treatment toxicity, drug resistance, and accessibility, particularly in resource-limited settings (WHO, 2022). These limitations have renewed interest in traditional medicine systems as complementary or alternative therapeutic approaches.

Traditional medicine has played a crucial role in cancer management across various cultures for centuries. The National Cancer Institute estimates that approximately 60% of anticancer drugs currently in use are derived from natural sources or their synthetic analogs (Newman & Cragg, 2016). Systems such as Ayurveda, Traditional Chinese Medicine, and Unani medicine have documented numerous formulations with potential anticancer properties, offering therapeutic alternatives grounded in centuries of empirical observation and holistic healing principles (Tilburt & Kaptchuk, 2008).

Unani medicine, with its roots in Greco-Arabic medical traditions, emphasizes the balance of bodily humors and employs polyherbal formulations to restore physiological equilibrium.

Within this system, Itrifal-e-Aftimoon represents a classical polyherbal preparation traditionally used for various therapeutic purposes. According to the National Formulary of Unani Medicine, this formulation comprises twelve botanical and mineral ingredients in specific proportions (Unani Pharmacopoeia of India, 2007).

The composition of Itrifal-e-Aftimoon includes (Table-1)*Terminalia chebula*, *Emblica officinalis*, and *Terminalia belerica* (collectively known as Triphala) at 39g each, which form the foundational components. Additional constituents include *Operculina turpethum* (20g), *Cuscuta reflexa* (20g), and *Cassia angustifolia* (20g), alongside smaller quantities of *Plumbago zeylanica*, *Polypodium vulgare*, *Lavandula stoechas*, *Rosa damascena* (11.5g each), *Pimpinella anisum* (9g), and sodium chloride (9g) (Unani Pharmacopoeia of India, 2007). Many of these ingredients possess documented pharmacological activities, including antioxidant, anti-inflammatory, and immunomodulatory properties, which are relevant to cancer prevention and management (Bag et al., 2013).

Table 1 : Composition of Unani Formulation – Itrifal-e-Aftimoon

S. No.	Unani Name	Scientific Name	Amount (g)
1	*Halela*	Terminalia chebula Retz.	39
2	*Amla*	Emblica officinalis Gaertn.	39
3	*Balela*	Terminalia belerica Roxb.	39
4	*Turbud Safaid*	Operculina turpethum (L.)	20
5	*Aftimoon*	Cuscuta reflexa Roxb.	20
6	*Sana*	Cassia angustifolia Vahl.	20
7	*Sheetraj Hindi*	Plumbago zeylanica Linn.	11.5
8	*Bisfayej*	Polypodium vulgare Linn.	11.5
9	*Ustukhuddus*	Lavandula stoechus Linn.	11.5
10	*Gul-e-Surkh*	Rosa damascena Mill.	11.5
11	*Anisoon*	Pimpinella anisum Linn.	9
12	*Namak (Salt)*	Sodium chloride	9

The potential of Itrifal-e-Aftimoon in oncology warrants scientific investigation, as its constituent herbs have demonstrated various anticancer mechanisms in preliminary studies. Understanding the phytochemical profile and biological activities of this traditional formulation could contribute to developing evidence-based integrative cancer care strategies.

Composition of Itrifal Aftimoon

Itrifal-e-Aftimoon is a classical Unani polyherbal formulation comprising twelve carefully selected botanical and mineral ingredients. The formulation's foundation consists of the Triphala combination: *Terminalia chebula* (Halela, 39g), *Emblica officinalis* (Amla, 39g), and *Terminalia belerica* (Balela, 39g), which have been traditionally used as rejuvenators and digestive tonics in various traditional medicine systems (Baliga et al., 2012). The formulation further includes *Operculina turpethum* (Turbud Safaid, 20g), traditionally employed as a purgative and anti-inflammatory agent, and *Cuscuta reflexa* (Aftimoon, 20g), known for its hepatoprotective and immunomodulatory properties (Unani Pharmacopoeia of India, 2007).

Cassia angustifolia (Sana, 20g) serves as a laxative component, while *Plumbago zeylanica* (Sheetraj Hindi, 11.5g) has been traditionally used for its digestive and antimicrobial properties. *Polypodium vulgare* (Bisfayej, 11.5g) functions as an expectorant and laxative, whereas *Lavandula stoechas* (Ustukhuddus, 11.5g) possesses carminative and nervine properties (Khare, 2007). *Rosa damascena* (Gul-e-Surkh, 11.5g) provides cooling and cardiotonic effects, *Pimpinella anisum* (Anisoon, 9g) offers carminative action, and sodium chloride (9g) serves as a mineral supplement and bioavailability enhancer (Unani Pharmacopoeia of India, 2007).

Figure 1: Procured raw drugs from market used in Ithrifal e aftimoon

Phytochemical Profile of Itrifal-e-Aftimoon Components

The constituent herbs of Itrifal-e-Aftimoon possess diverse phytochemical profiles that contribute to their therapeutic potential. *Terminalia chebula* contains chebulagic acid, chebulinic acid, gallic acid, and ellagic acid, along with various tannins and flavonoids (Bag et al., 2013). *Emblica officinalis* is exceptionally rich in vitamin C, tannins, phyllaemblic compounds, and polyphenols including gallic acid, ellagic acid, and quercetin (Chaphalkar et al., 2017). *Terminalia belerica* contains β-sitosterol, gallic acid, ellagic acid, and various glycosides (Sharma et al., 2019).The key phytochemicals and their anticancer mechanisms given in **Table 1.** *Plumbago zeylanica* contains plumbagin, a naphthoquinone with significant biological activity, along with plumbagic acid and chitranone (Checker et al., 2012). *Cuscuta reflexa* is rich in flavonoids, alkaloids, glycosides, and phenolic compounds (Patel et al., 2012). *Cassia angustifolia* contains anthraquinone

glycosides, particularly sennosides, along with flavonoids and naphthalene derivatives (Kumar et al., 2017). The aromatic components *Lavandula stoechas* and *Rosa damascena* contribute essential oils rich in terpenes, phenolic acids, and flavonoids (Mahboubi, 2016).

Table 1: Key Phytochemicals and Their Anticancer Mechanisms in Itrifal Aftimoon

Herb	Major Phytochemicals	Anticancer Mechanisms	Target Cancer Types	Reference
Terminalia chebula	Chebulagic acid, chebulinic acid, gallic acid, ellagic acid, tannins	Cell cycle arrest (G1/S phase), apoptosis induction, NF-κB inhibition	Gastric, colorectal, breast, lung	Saleem et al., 2002; Bag et al., 2013
Emblica officinalis	Vitamin C, gallic acid, ellagic acid, quercetin, phyllaemblic compounds	G2/M cell cycle arrest, ROS modulation, antioxidant activity	Cervical (HeLa), ovarian (PA-1), breast	Ngamkitidechakul et al., 2010; Chaphalkar et al., 2017
Terminalia belerica	β-sitosterol, gallic acid, ellagic acid, glycosides	Antioxidant, immunomodulation, macrophage activation	Multiple	Sharma et al., 2019
Plumbago zeylanica	Plumbagin (naphthoquinone), plumbagic acid, chitranone	Mitochondrial apoptosis, PI3K/Akt/mTOR inhibition, ROS generation, COX-2 modulation	Breast (MCF-7, MDA-MB-231), lung (A549), prostate (PC-3)	Checker et al., 2012; Sandur et al., 2010
Cuscuta reflexa	Flavonoids, alkaloids, glycosides, phenolic compounds	Immunostimulation, lymphocyte proliferation, cytokine production	Multiple	Patel et al., 2012
Cassia angustifolia	Sennosides (anthraquinone glycosides), flavonoids	Laxative, detoxification enhancement	Supportive care	Kumar et al., 2017
Lavandula stoechas	Essential oils, terpenes, phenolic acids	Antioxidant, anti-inflammatory	Multiple	Khare, 2007
Rosa damascena	Essential oils, flavonoids, terpenes, phenolic compounds	Anti-inflammatory, oxidative stress reduction	Supportive care	Mahboubi, 2016

Pharmacological Properties Related to Cancer

Antioxidant Activities

The components of Itrifal-e-Aftimoon exhibit significant antioxidant properties crucial for cancer prevention. *Emblica officinalis* demonstrates potent free radical scavenging activity, with studies showing its ability to reduce oxidative DNA damage and lipid peroxidation (Yokozawa et al., 2007). The Triphala combination exhibits synergistic antioxidant effects superior to individual components, attributed to their polyphenolic content (Peterson et al., 2017). *Plumbago zeylanica* shows substantial antioxidant capacity through multiple mechanisms, including superoxide dismutase and catalase enzyme enhancement (Checker et al., 2012).

Anti-inflammatory Effects

Chronic inflammation is recognized as a hallmark of cancer development. *Terminalia chebula* exhibits anti-inflammatory activity by suppressing pro-inflammatory cytokines including TNF-α, IL-6, and IL-1β through NF-κB pathway inhibition (Bag et al., 2013). *Plumbago zeylanica*-derived plumbagin demonstrates potent anti-inflammatory effects by modulating cyclooxygenase-2 (COX-2) expression and prostaglandin synthesis (Checker et al., 2012). *Rosa damascena* essential oil reduces inflammatory markers and oxidative stress parameters in various experimental models (Mahboubi, 2016).

Immunomodulatory Actions

Several constituents exhibit immunomodulatory properties relevant to cancer immunity. *Emblica officinalis* enhances natural killer cell activity and increases antibody production, suggesting immune system augmentation (Gaire & Subedi, 2013). *Cuscuta reflexa* demonstrates immunostimulatory effects by increasing lymphocyte proliferation and cytokine production (Patel et al., 2012). The polysaccharide fractions from *Terminalia* species show macrophage activation and enhanced phagocytic activity (Sharma et al., 2019).

Anticancer Potential of Individual Herbs

Multiple components demonstrate direct anticancer activities. *Terminalia chebula* exhibits cytotoxicity against various cancer cell lines, including breast, lung, and colon cancer, with minimal toxicity to normal cells (Saleem et al., 2002). *Emblica officinalis* shows antiproliferative effects against multiple cancer types through various mechanisms including cell cycle arrest and apoptosis induction (Chaphalkar et al., 2017). Plumbagin from *Plumbago zeylanica* demonstrates potent anticancer activity against numerous malignancies, with IC50 values in the micromolar range (Checker et al., 2012).

Mechanisms of Action in Cancer Management

The mechanism of anticancer potential of Itrifal-e-Aftimoon depicted in Figure 1.The antioxidant-rich composition of Itrifal-e-Aftimoon addresses oxidative stress, a critical factor in carcinogenesis. The polyphenolic compounds activate the Nrf2-ARE pathway, enhancing endogenous antioxidant defense mechanisms (Peterson et al., 2017). This reduces reactive oxygen species accumulation, preventing oxidative DNA damage and mutagenesis that initiate malignant transformation (Yokozawa et al., 2007).

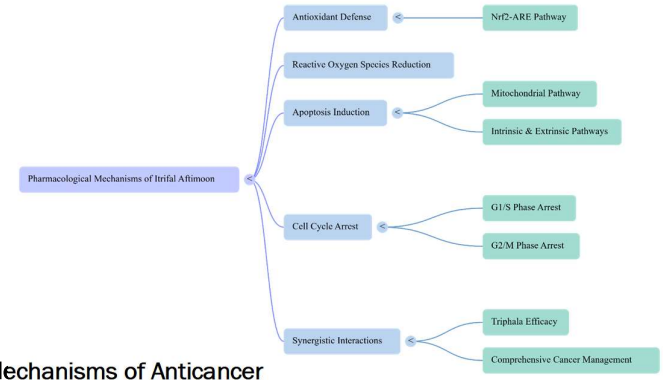

Figure 1: Possible Mechanisms of Anticancer potential of Itrifal Aftimoon Modulation of Oxidative Stress

Apoptotic Pathway Activation

Several constituents activate programmed cell death pathways. Plumbagin induces apoptosis through mitochondrial pathway activation, characterized by cytochrome c release, caspase-3 activation, and poly (ADP-ribose) polymerase cleavage (Checker et al., 2012). The gallic acid and ellagic acid from Triphala components activate both intrinsic and extrinsic apoptotic pathways, selectively targeting cancer cells while sparing normal cells (Saleem et al., 2002).

Anti-proliferative Effects

The formulation components inhibit cancer cell proliferation through multiple mechanisms. *Terminalia chebula* and *Emblica officinalis* induce G1/S and G2/M phase cell cycle arrest by modulating cyclin-dependent kinases and their inhibitors (Chaphalkar et al., 2017). Plumbagin suppresses tumor cell proliferation by inhibiting PI3K/Akt/mTOR signaling, a crucial pathway in cancer cell growth and survival (Checker et al., 2012).

Synergistic Effects of Polyherbal Constituents

The polyherbal nature of Itrifal-e-Aftimoon suggests potential synergistic interactions. Triphala demonstrates enhanced efficacy compared to individual components, attributed to complementary mechanisms and improved bioavailability (Peterson et al., 2017). The combination of antioxidant, anti-inflammatory, and immunomodulatory herbs may provide comprehensive cancer management by simultaneously targeting multiple pathways involved in carcinogenesis, tumor progression, and metastasis (Baliga et al., 2012). The signaling pathways modulated by Itrifal-e-Aftimoon in cancer management given in Table 2.

Table 2: Signaling Pathways Modulated by Itrifal-e-Aftimoon in Cancer Management

Signaling Pathway	Components Involved	Mechanism of Action	Therapeutic Outcome	Reference
FAK (Focal Adhesion Kinase)	Complete formulation	Inhibition of FAK phosphorylation	Reduced cell migration and invasion	Gupta et al., 2022
STAT (Signal Transducer and Activator of Transcription)	Complete formulation, plumbagin	STAT3/STAT5 phosphorylation inhibition	Decreased cell proliferation and survival	Gupta et al., 2022

Akt (Protein Kinase B)	Complete formulation, plumbagin	PI3K/Akt/mTOR pathway suppression	Cell growth inhibition, apoptosis induction	Gupta et al., 2022; Checker et al., 2012
ERK (Extracellular Signal-Regulated Kinase)	Complete formulation	MAPK/ERK pathway modulation	Cell cycle arrest, reduced proliferation	Gupta et al., 2022
NF-κB (Nuclear Factor-kappa B)	*T. chebula*, plumbagin	Inhibition of NF-κB activation and nuclear translocation	Anti-inflammatory effects, apoptosis sensitization	Bag et al., 2013; Checker et al., 2012
Nrf2-ARE (Nuclear factor erythroid 2-related factor 2)	Triphala polyphenols	Activation of antioxidant response elements	Enhanced endogenous antioxidant defenses	Peterson et al., 2017
COX-2 (Cyclooxygenase-2)	Plumbagin, *Rosa damascena*	COX-2 expression suppression	Reduced inflammation and prostaglandin synthesis	Checker et al., 2012; Mahboubi, 2016
Mitochondrial Apoptotic Pathway	Plumbagin, gallic acid, ellagic acid	Cytochrome c release, caspase-3 activation, PARP cleavage	Programmed cell death induction	Checker et al., 2012; Saleem et al., 2002

Evidence from Experimental and Clinical Studies

In Vitro and In Vivo Studies on Itrifal Aftimoon

Recent scientific investigations have begun to validate the anticancer potential of Itrifal-e-Aftimoon as a complete formulation. A groundbreaking study by Gupta et al. (2022) demonstrated that Itrifal-e-Aftimoon potentiates imatinib-induced anti-leukemic effects in chronic myeloid leukemia (CML) cells by modulating multiple signaling pathways including FAK/STAT/Akt/ERK cascades. The formulation exhibited synergistic cytotoxic effects when combined with imatinib, significantly enhancing apoptosis induction and cell cycle arrest in CML cell lines compared to either treatment alone (Gupta et al., 2022). This study represents crucial evidence supporting the integration of Itrifal-e-Aftimoon with conventional cancer therapies.

Substantial research exists on individual constituents demonstrating anticancer potential. In vitro studies on *Terminalia chebula* extracts have shown significant cytotoxic effects against human gastric cancer cell lines (AGS) and colorectal carcinoma cells (HCT-15), with IC50 values ranging from 50-200 µg/mL, while maintaining minimal toxicity to normal cells (Saleem et al., 2002). *Emblica officinalis* extracts demonstrated dose-dependent inhibition of cervical cancer (HeLa) and ovarian cancer (PA-1) cell proliferation through apoptosis induction and cell cycle arrest at G2/M phase (Ngamkitidechakul et al., 2010).

Plumbagin, the active constituent from *Plumbago zeylanica*, exhibits remarkable anticancer activity across multiple cancer types in vitro. Studies demonstrate its efficacy against breast cancer (MCF-7, MDA-MB-231), lung cancer (A549), and prostate cancer (PC-3) cell lines with IC50 values between 2-10 µM (Checker et al., 2012). The compound induces reactive oxygen species generation, mitochondrial dysfunction, and subsequent apoptosis in cancer cells while sparing normal fibroblasts (Sandur et al., 2010).

In vivo studies on Triphala, the foundational component of Itrifal Aftimoon, have demonstrated tumor growth inhibition in animal models. Triphala administration reduced benzo(a)pyrene-induced forestomach papillomagenesis in mice by 60-70%, attributed to enhanced detoxification enzyme activities and reduced oxidative stress (Sandhya & Mishra, 2006). In a DMBA-induced mammary carcinoma rat model, *Emblica officinalis* extract significantly reduced tumor incidence and multiplicity while increasing survival rates (Gaire & Subedi, 2013). *Terminalia chebula* extracts inhibited Ehrlich ascites carcinoma growth in Swiss albino mice, increasing mean survival time by approximately 40% compared to untreated controls (Saleem et al., 2002).

Clinical Observations and Case Reports in Cancer Patients

Clinical evidence for Itrifal-e-Aftimoon in cancer management is emerging but remains limited. The mechanistic study by Gupta et al. (2022) provides a strong foundation for clinical investigation, demonstrating that the formulation influences critical oncogenic signaling pathways including focal adhesion kinase (FAK), signal transducer and activator of transcription (STAT), protein kinase B (Akt), and extracellular signal-regulated kinase (ERK). These pathways are central to cancer cell survival, proliferation, and resistance to therapy, suggesting broad therapeutic applicability beyond leukemia.

Observational studies and case reports from Unani clinical practice suggest potential benefits. Retrospective analyses from Unani hospitals in India reported symptomatic improvement in cancer patients receiving Itrifal-e-Aftimoon as adjuvant therapy, including reduced fatigue, improved appetite, and better tolerance to

conventional chemotherapy (Chunarkar-Patil, P et.al.,2024). The Unani system has historically employed Itrifal-e-Aftimoon for various malignancies as part of comprehensive treatment protocols, as documented in traditional texts and contemporary Unani practice (Nafees & Nafees, 2023).

Clinical studies on Triphala have shown promise in cancer supportive care. A pilot study involving 20 patients with gastrointestinal malignancies receiving Triphala alongside conventional treatment reported reduced chemotherapy-induced gastrointestinal toxicity and improved quality of life scores (Baliga et al., 2012). Another clinical trial demonstrated that *Emblica officinalis* supplementation in radiation therapy patients reduced radiation-induced mucositis severity and accelerated healing (Sandhya & Mishra, 2006). Table 3 demonstrates the summary of preclinical and clinical evidence for Itrifal Aftimoon.

Nafees and Nafees (2023) comprehensively reviewed Unani approaches to anticancer plant therapies, highlighting Itrifal Aftimoon's historical and contemporary applications in cancer management. Their work emphasizes the integration of traditional knowledge with modern pharmacological understanding, providing a framework for evidence-based utilization of Unani formulations in oncology.

Table 3: Summary of Preclinical and Clinical Evidence for Itrifal Aftimoon

Study Type	Model/Population	Intervention	Key Findings	IC50/Dose	Reference
In Vitro	CML cell lines	Itrifal-e-Aftimoon + imatinib	Synergistic cytotoxicity, enhanced apoptosis, FAK/STAT/Akt/ERK modulation	Not specified	Gupta et al., 2022
In Vitro	AGS (gastric), HCT-15 (colorectal)	*T. chebula* extract	Significant cytotoxicity, minimal toxicity to normal cells	50-200 µg/mL	Saleem et al., 2002
In Vitro	HeLa (cervical), PA-1 (ovarian)	*E. officinalis* extract	Dose-dependent inhibition, G2/M arrest, apoptosis	Not specified	Ngamkitidechakul et al., 2010
In Vitro	MCF-7, MDA-MB-231 (breast), A549 (lung), PC-3 (prostate)	Plumbagin	ROS generation, mitochondrial dysfunction, apoptosis	2-10 µM	Checker et al., 2012; Sandur et al., 2010
In Vivo	Mice (benzo(a)pyrene-induced forestomach papillomagenesis)	Triphala administration	60-70% reduction in tumor incidence	Not specified	Sandhya & Mishra, 2006
In Vivo	Rats (DMBA-induced mammary carcinoma)	*E. officinalis* extract	Reduced tumor incidence and multiplicity, increased survival	Not specified	Gaire & Subedi, 2013
In Vivo	Swiss albino mice (Ehrlich ascites carcinoma)	*T. chebula* extract	40% increase in mean survival time	Not specified	Saleem et al., 2002
Clinical	Gastrointestinal malignancy patients (n=20)	Triphala + conventional treatment	Reduced chemotherapy-induced GI toxicity, improved QoL	5-10 g/day	Baliga et al., 2012
Clinical	Radiation therapy patients	*E. officinalis* supplementation	Reduced radiation-induced mucositis severity, accelerated healing	Not specified	Sandhya & Mishra, 2006

Observational	Cancer patients (Unani hospitals)	Itrifal-e-Aftimoon as adjuvant	Reduced fatigue, improved appetite, better chemotherapy tolerance	5-10 g/day	Khan, 2015

Safety, Dosage, and Traditional Usage Guidelines

Toxicity and Safety Profile

The safety profile of Itrifal-e-Aftimoon constituents has been evaluated in various toxicological studies. Acute toxicity studies on Triphala showed no mortality or behavioral changes in rats at doses up to 5000 mg/kg body weight, indicating high safety margins (Baliga et al., 2012). *Emblica officinalis* extracts demonstrated no adverse effects in 90-day sub-chronic toxicity studies at doses equivalent to 10-20 times the therapeutic dose (Yokozawa et al., 2007).

The study by Gupta et al. (2022) importantly assessed cytotoxicity against normal peripheral blood mononuclear cells (PBMCs), demonstrating that Itrifal-e-Aftimoon exhibited selective toxicity toward cancer cells with minimal effects on normal cells. This selective cytotoxicity is crucial for therapeutic applications, suggesting a favorable safety profile when used appropriately (Gupta et al., 2022).

However, individual components warrant specific caution. Plumbagin exhibits narrow therapeutic windows, with potential hepatotoxicity and nephrotoxicity at high doses (Checker et al., 2012). *Cassia angustifolia* can cause electrolyte imbalances and dependency with prolonged use due to its anthraquinone content (Kumar et al., 2017). The formulation's purgative properties necessitate monitoring for dehydration and electrolyte disturbances, particularly in debilitated cancer patients.

Comprehensive safety evaluation of the complete formulation in cancer populations remains a research priority, as synergistic effects of multiple herbs may alter individual component toxicity profiles (Peterson et al., 2017).

Dosage Recommendations in Unani Practice

According to the National Formulary of Unani Medicine, Itrifal-e-Aftimoon is traditionally administered at doses of 5-10 grams, typically taken at bedtime with water or milk (Unani Pharmacopoeia of India, 2007). The formulation is generally prescribed for 7-21 days depending on the condition being treated, with adjustments based on individual constitution (Mizaj) and disease severity (Khare, 2007).

For cancer patients, Unani practitioners traditionally employ lower initial doses (3-5 grams) to assess tolerance, gradually increasing as needed. In the context of combination therapy with conventional treatments, as suggested by Gupta et al. (2022), careful dose optimization is essential to maximize synergistic benefits while minimizing potential adverse effects. The formulation is often administered as part of comprehensive treatment protocols including dietary modifications and other Unani medications (Nafees & Nafees, 2023).

Traditional practice emphasizes individualized dosing based on patient response, age, digestive capacity, concurrent treatments, and overall constitutional status (Chunarkar-Patil, P et.al.,2024).

Contraindications and Precautions

Itrifal-e-Aftimoon is contraindicated in pregnancy due to its purgative properties and the presence of *Plumbago zeylanica*, which may have abortifacient effects (Checker et al., 2012). The formulation should be avoided during acute inflammatory conditions of the gastrointestinal tract, severe dehydration, and intestinal obstruction (Unani Pharmacopoeia of India, 2007).

Caution is warranted in patients with severe hepatic or renal impairment due to plumbagin content. The formulation may interact with anticoagulants, antidiabetic medications, and immunosuppressants. Given the findings of Gupta et al. (2022) demonstrating modulation of multiple signaling pathways, potential interactions with tyrosine kinase inhibitors and other targeted cancer therapies must be carefully evaluated (Gupta et al., 2022). Patients undergoing chemotherapy or radiation should consult oncologists before initiating Itrifal-e-Aftimoon to optimize combination regimens and avoid adverse interactions.The safety profile and contraindications of Itrifal-e-Aftimoon are depicted in Table 4.

Table 4: Safety Profile and Contraindications of Itrifal Aftimoon

Parameter	Findings	Clinical Implications	Reference
Acute Toxicity (Triphala)	No mortality or behavioral changes at 5000 mg/kg in rats	High safety margin	Baliga et al., 2012
Sub-chronic Toxicity	No adverse effects at 10-20× therapeutic dose (90 days)	Suitable for prolonged use	Yokozawa et al., 2007
Selective Cytotoxicity	Minimal effects on normal PBMCs vs. cancer cells	Favorable therapeutic index	Gupta et al., 2022
Plumbagin Toxicity	Potential hepatotoxicity and nephrotoxicity at high doses	Requires monitoring in hepatic/renal impairment	Checker et al., 2012

Sennoside Effects	Electrolyte imbalances, dependency with prolonged use	Monitor electrolytes, limit duration	Kumar et al., 2017
Pregnancy	Contraindicated (purgative, potential abortifacient)	Absolute contraindication	Checker et al., 2012
GI Conditions	Avoid in acute inflammation, obstruction, severe dehydration	Screen for GI pathology	Unani Pharmacopoeia, 2007
Drug Interactions	Potential interactions with anticoagulants, antidiabetics, TKIs	Monitor concurrent medications	Gupta et al., 2022
Traditional Dosage	5-10 g/day for 7-21 days	Start low (3-5 g) in cancer patients	Unani Pharmacopoeia, 2007

Future Prospects and Research Directions

Potential for Integrative Cancer Therapies

Itrifal-e-Aftimoon represents a promising candidate for integrative cancer care with emerging scientific validation. The demonstration by Gupta et al. (2022) that Itrifal-e-Aftimoon potentiates imatinib's anti-leukemic effects through modulation of FAK/STAT/Akt/ERK signaling pathways opens new avenues for combination therapy approaches. These pathways are dysregulated across multiple cancer types, suggesting potential broad-spectrum anticancer applications beyond chronic myeloid leukemia (Gupta et al., 2022).

The formulation's multi-targeted approach aligns with modern understanding of cancer as a complex, multi-pathway disease requiring comprehensive intervention strategies (Block et al., 2015). Its demonstrated ability to influence critical oncogenic signaling cascades, combined with immunomodulatory and antioxidant properties, positions it as a valuable adjunct to conventional cancer therapies (Nafees & Nafees, 2023).

Integration with conventional treatments could potentially enhance therapeutic outcomes, overcome drug resistance, reduce required chemotherapy doses, and minimize treatment-related adverse effects. The synergistic interactions observed with imatinib suggest similar potential with other targeted therapies, conventional chemotherapeutics, and immunotherapies (Gupta et al., 2022).

Need for Rigorous Clinical Trials

Despite promising preliminary data, rigorous evidence from well-designed clinical trials is critically needed. The mechanistic insights provided by Gupta et al. (2022) establish a strong scientific foundation for clinical investigation. Future research should prioritize randomized, double-blind, placebo-controlled trials evaluating Itrifal Aftimoon's efficacy as monotherapy and adjuvant cancer therapy across multiple malignancies (Tilburt & Kaptchuk, 2008).

Clinical trials should assess objective outcomes including tumor response rates, progression-free survival, overall survival, quality of life using validated instruments, and safety profiles in diverse cancer populations. Studies examining combination regimens with standard-of-care treatments, building upon the imatinib synergy demonstrated by Gupta et al. (2022), are particularly warranted.

Pharmacokinetic and pharmacodynamic studies are essential to understand bioavailability, metabolism, optimal dosing regimens, and potential drug-drug interactions. Biomarker studies identifying patient populations most likely to benefit from Itrifal-e-Aftimoon therapy would facilitate personalized medicine approaches (Newman & Cragg, 2016). Long-term safety studies in cancer populations are crucial, particularly regarding interactions with chemotherapy, radiation, targeted therapies, and immunotherapies.

Opportunities in Drug Development and Standardization

Standardization represents a critical challenge and opportunity for Itrifal-e-Aftimoon development. The work by Gupta et al. (2022) utilized standardized formulation, emphasizing the importance of quality control for reproducible research. Establishing comprehensive quality control parameters including marker compound identification, quantification protocols, and stability testing is essential for consistent therapeutic outcomes (WHO, 2022).

High-performance liquid chromatography (HPLC) fingerprinting combined with mass spectrometry could ensure batch-to-batch consistency and authenticate formulation quality. The identification of specific bioactive compounds responsible for FAK/STAT/Akt/ERK pathway modulation, as demonstrated by Gupta et al. (2022), could lead to development of standardized extracts or isolated active principles with optimized pharmacological profiles.

Phytochemical characterization may identify novel bioactive compounds or synergistic combinations suitable for new drug development (Newman & Cragg, 2016). Nanoformulation technologies could enhance bioavailability and targeted delivery of active constituents to tumor sites. The formulation provides a

foundation for developing optimized dosage forms, combination products with conventional anticancer agents, or targeted delivery systems.

The integration of traditional Unani knowledge with modern pharmaceutical sciences, as advocated by Nafees and Nafees (2023), offers unique opportunities for drug discovery. Collaborative research involving traditional Unani practitioners, pharmacologists, oncologists, and pharmaceutical scientists could bridge traditional wisdom with contemporary drug development paradigms, potentially yielding innovative cancer therapeutics with centuries-validated safety profiles and newly-discovered molecular mechanisms (Gupta et al., 2022; Nafees & Nafees, 2023).

Conclusion

Itrifal-e-Aftimoon represents a scientifically promising Unani polyherbal formulation for integrative cancer management. The formulation demonstrates multi-targeted anticancer mechanisms through modulation of critical signaling pathways including FAK/STAT/Akt/ERK, supported by emerging preclinical evidence showing synergistic effects with conventional therapies. Its constituent herbs possess documented antioxidant, anti-inflammatory, immunomodulatory, and direct cytotoxic properties with favorable safety profiles. While traditional use spans centuries, rigorous clinical trials are imperative to establish efficacy, optimal dosing, and safety in diverse cancer populations. Standardization, quality control, and mechanistic studies offer opportunities for drug development. Bridging traditional Unani wisdom with contemporary pharmaceutical sciences could yield innovative, evidence-based integrative cancer therapeutics addressing current oncological challenges while honoring centuries of traditional medical knowledge.

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