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"Therapeutic Potential of Picrorhiza kurroa and Piper longum in High-Fat Diet-Induced Insulin Resistance, Metabolic Syndrome, and Non-Alcoholic Fatty Liver Disease: A Case Study"

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ABSTRACT

This study investigates the therapeutic potential of 'Picrorhiza kurroa' and 'Piper longum' in ameliorating the complex pathological manifestations associated with high-fat diet-induced insulin resistance, metabolic syndrome, and non-alcoholic fatty liver disease. Specifically, this study examines the efficacy of these traditional medicinal plants in modulating key biochemical and physiological markers relevant to hepatic steatosis, glucose dysregulation, and systemic metabolic dysfunction.

Methodology: This study employed a comprehensive approach to evaluate the therapeutic effects, integrating clinical observations with relevant laboratory investigations. The assessment included detailed anthropometric measurements, biochemical analyses of liver function, lipid profiles, and glucose homeostasis, alongside imaging modalities to quantify hepatic steatosis. The therapeutic intervention involved a standardized preparation of 'Picrorhiza kurroa' and 'Piper longum', administered over a defined period, with outcomes rigorously monitored against baseline data.

Finding: Following the intervention, significant improvements were observed across several metabolic parameters, including a reduction in hepatic steatosis as quantified by imaging, and favorable shifts in lipid profiles and glucose homeostasis. These improvements suggest a potential for 'Picrorhiza kurroa' and 'Piper longum' to mitigate aspects of metabolic syndrome and non-alcoholic fatty liver disease, possibly through mechanisms involving the modulation of lipid accumulation and insulin sensitivity.

Implication: These findings underscore the need for further rigorous investigation into the specific phytoconstituents responsible for these effects, particularly picroside II from 'Picrorhiza kurroa' and 'Piper longum', which have demonstrated hepatoprotective and anti-hyperlipidemic properties, respectively.

Originality/Value: This research provides preliminary insights into the potential of combined herbal interventions for multifaceted metabolic disorders, advocating for larger-scale clinical trials to validate these promising effects

Keywords: Picrorhiza kurroa, Piper longum, high-fat diet, insulin resistance, metabolic syndrome, non-alcoholic fatty liver disease, hepatoprotective, lipid metabolism,glucose homeostasis.

INTRODUCTION

The escalating global prevalence of metabolic syndrome and non-alcoholic fatty liver disease, largely driven by sedentary lifestyles and Westernized dietary patterns, underscores an urgent need for effective therapeutic strategies. While conventional treatments often focus on symptom management and lifestyle modifications, their limitations highlight the imperative to explore novel interventions, including those derived from traditional medicine systems such as Ayurveda. Indeed, phytochemicals from medicinal plants have garnered increasing scientific attention for their potential therapeutic activities and safety profiles in both preclinical and clinical settings (Dhami-Shah et al., 2017). Specifically, Picrorhiza kurroa has demonstrated efficacy in ameliorating various pathological conditions, including non-alcoholic fatty liver disease, through mechanisms that warrant further elucidation. Similarly, Piper longum, rich in piperine, exhibits promising pharmacological properties,

including anti-inflammatory, lipid-lowering, and insulin-sensitizing effects, which are particularly relevant for managing metabolic disorders. Piperine, a major constituent of Piper longum, has been shown to improve insulin signaling and normalize plasma parameters of oxidative stress and inflammation in high-fat diet-induced hepatic steatosis (Tripathi et al., 2022). Moreover, piperine has been demonstrated to regulate hepatic energy metabolism by modulating fatty acid metabolism through alterations in gut microbiota composition, specifically by increasing the abundance of short-chain fatty acid-producing bacteria.

Existing studies have also indicated that piperine, a key alkaloid in Piper longum, exerts anti-obesity effects by modulating body composition and lipid profiles in high-fat diet-induced obese rats (Meriga et al., 2017). Such evidence suggests the potential of piperine not only as a standalone therapeutic agent but also as a bioavailability enhancer for other phyto-complexes, thereby increasing the efficacy of co-administered compounds. The present case study aims to investigate the synergistic therapeutic potential of Picrorhiza kurroa and Piper longum in a high-fat diet-induced model of insulin resistance, metabolic syndrome, and non-alcoholic fatty liver disease, thereby addressing a critical gap in the literature regarding their combined efficacy.

Despite the individual pharmacological profiles of *P. kurroa* and *P. longum*, their combined effect on the intricate interplay of insulin resistance, dyslipidemia, and hepatic steatosis, particularly in a human context, remains largely unexplored. This single case study, therefore, seeks to provide initial clinical insights into their combined therapeutic utility in mitigating these multifaceted metabolic derangements. The current investigation thus aimed to evaluate the integrated impact of these traditional botanical agents on specific biomarkers associated with metabolic syndrome and non-alcoholic fatty liver disease, thereby establishing a foundation for subsequent comprehensive clinical trials.

2. CASE PRESENTATION

2.1Patient Information

A 35-year-old male presented with complaints of dull abdominal pain, reduced appetite, and general discomfort for the past two months. The patient had a known history of dyslipidemia and impaired glucose tolerance. His lifestyle was predominantly sedentary, with a diet rich in saturated fats and refined carbohydrates. Family history revealed type 2 diabetes mellitus and hypertension in both parents, suggesting a genetic predisposition to metabolic disorders.

2.2 Clinical Findings

On physical examination, the patient exhibited central obesity with a body weight of 92 kg, waist circumference of 108 cm and a BMI of 30.5 kg/m². No significant abnormalities were observed in cardiovascular or respiratory systems.

2.3 Diagnostic Assessment

Baseline investigations revealed:

Elevated liver enzymes (ALT, AST)

Increased fasting blood glucose (FBS) and HbA1c

Dyslipidemia (elevated total cholesterol, LDL, triglycerides; reduced HDL)

Ultrasonography of the abdomen confirmed Grade II hepatic steatosis, consistent with non-alcoholic fatty liver disease (NAFLD).

2.4 Intervention

The patient was administereda herbal formulation consisting of standardized extract of *Picrorhiza kurroa* and *Piper longum*. The formulation was given in a 3:2 ratio, with a total dose of 500 mg twice daily for three months.Throughout this period, compliance was monitored through patient self-reporting and regular follow-up consultations to ensure fidelity to the prescribed regimen.

2.5 Diet and Lifestyle

In addition to herbal therapy, the patient was advised hypocaloric diet emphasizing whole foods, reduction of refined sugars and saturated fats, regular physical activity (walking 1–2 hours/day, 4-5 days/week).

3. TIMELINE OF THE TREATMENT

The patient had treatment for three months. The timeline of thetreatment is presented in Table 1.

Table 1: Timeline of the treatment

Health Event	Timeline
Baseline investigations	December 29th, 2023 (Elevated ALT/AST, fasting glucose, HbA1c; dyslipidemia (↑total cholesterol, LDL, triglycerides; ↓HDL); abdominal ultrasonography showed Grade II hepatic steatosis)
Visited for Ayurveda treatment	January 08th, 2024
Clinical assessment and examination	January 08th, 2024 (Reduced appetite, dull pain in abdomen, central obesity, weight 92 kg, waist circumference 108 cm, BMI 30.5 kg/m²), cardiovascular and respiratory examination within normal limits)
Initiation of treatment	January 10th, 2024 (Standardized herbal extract of *Picrorhiza kurroa* and *Piper longum* (3:2 ratio), 500 mg twice daily for 3 months; compliance monitored through self-reporting and follow-up visits)
Post treatment investigations performed	April 16th, 2024

4. RESULTS

The outcomes assessed included changes in liver enzyme levels, fasting glucose, HbA1c, lipid panel (total cholesterol, LDL-C, triglycerides,HDL-C), alongside ultrasonographic assessments of hepatic steatosis and anthropometric measurements.

4.1Improvements in Insulin Sensitivity and Glucose Metabolism

Post-intervention, significant improvements were noted in fasting blood glucose, indicating enhanced systemic insulin sensitivity. Specifically, fasting glucose decreased from 145 mg/dL to 102 mg/dL, and HbA1c reduced from 7.8% to 6.1%, moving the patient from diabetic to pre-diabetic ranges.This amelioration in glucose homeostasis suggests a substantial reversal of the insulin resistance component of his metabolic syndrome, which is often a key driver of non-alcoholic fatty liver disease progression. Furthermore, a marked reduction in glycosylated hemoglobin (HbA1c) was observed, reflecting improved long-term glycemic control.

4.2Alterations in Lipid Profile

The lipid profile also demonstrated notable enhancements, with significant decreases in total cholesterol, LDL-c, and triglycerides, coupled with an increase in HDL-c, indicating a positive modulation of dyslipidemia crucial for mitigating cardiovascular risk and hepatic steatosis progression.Specifically, total cholesterol decreased from 240 mg/dL to 186 mg/dL, LDL-c from 162 mg/dL to 100 mg/dL, triglycerides from 260 mg/dL to 148 mg/dL, and HDL-c increased from 35 mg/dL to 45 mg/dL, all contributing to a more favorable cardiovascular risk profile.

4.3Hepatic Function and Imaging Findings

Evaluation of liver enzymes revealed a substantial reduction in both alanine aminotransferase and aspartate aminotransferase levels, signaling a decrease in hepatocellular injury. The hepatic function and Imaging findings section details that alanine aminotransferase levels decreased from 85 U/L to 32 U/L, and aspartate aminotransferase levels reduced from 70 U/L to 28 U/L, approaching healthy reference ranges. Furthermore, follow-up abdominal ultrasonography confirmed a regression from grade 2 to grade 1 hepatic steatosis.

4.4 Anthropometric Parameters

At the end of the twelve-week intervention, significant reductions were observed in body weight, waist circumference, and body mass index, reflecting a positive impact of the combined therapeutic strategy on overall adiposity. Specifically, the patient's weight decreased from 92 kg to 85 kg, his waist circumference reduced from 108 cm to 101 cm, and his BMI declined from 30.5 kg/m² to 28.2 kg/m², transitioning from obese to overweight classification.

4.5 Adverse Events and Tolerability

Throughout the twelve-week intervention, the patient reported no significant adverse events, and the herbal regimen was well-tolerated, indicating a favorable safety profile for the combined *Picrorhiza kurroa* and *Piper longum* extract at the prescribed dosage.

5.Discussion

Non-alcoholic fatty liver disease is increasingly encountered in routine clinical practice and is closely associated with metabolic syndrome, insulin resistance, and obesity. Although many cases remain asymptomatic, a significant proportion may progress to steatohepatitis, fibrosis, cirrhosis, and even hepatocellular carcinoma if left untreated (Fan et al., 2010). The growing burden of NAFLD highlights the need for safe and effective therapeutic interventions that address its multifactorial pathogenesis.

In the present case, a 35-year-old obese male with Grade II fatty liver, dyslipidemia, and impaired glucose metabolism was managed using a combination of Picrorhiza kurroa and Piper longum, along with dietary and lifestyle modifications. The clinical presentation of central obesity, altered lipid profile, hepatic steatosis, and insulin resistance observed in this patient is consistent with the pathophysiological spectrum of metabolic syndrome and NAFLD.

From an Ayurvedic perspective, the condition can be correlated with *YakritRoga* associated with *Medoroga*, where excessive intake of high-fat diet and sedentary lifestyle leads to vitiation of *Kapha* and *Meda* (Singhal et al., 2015). This results in impaired *Agni*, accumulation of *Ama*, and subsequent derangement of lipid metabolism, ultimately contributing to hepatic steatosis. A similar clinical picture was evident in the present case, where features of *Kapha-Meda Dushti* and *Agnimandya* were predominant.

The therapeutic approach adopted in this case primarily focused on correcting the underlying metabolic imbalance through principles of *Agni Deepana, Ama Pachana*, and *Medohara* (Kumar et al., 2021). Picrorhiza kurroa, characterized by *Tikta Rasa* predominance, is well-known for its hepatoprotective, anti-inflammatory, and lipid-lowering properties(Dhami-Shah et al., 2017). Its active constituents, particularly picrosides, have been reported to modulate hepatic lipid metabolism, reduce oxidative stress, and improve liver function. Additionally, Piper longum, rich in piperine, exerts significant bio-enhancing, anti-inflammatory, and insulin-sensitizing effects(Gani et al., 2019). Piperine has been shown to improve insulin signaling, regulate lipid metabolism, and modulate gut microbiota, thereby contributing to improved metabolic homeostasis.

The combination of these two drugs may also be understood in light of the Ayurvedic concept of *Yogavahi*, wherein Piper longum enhances the bioavailability and therapeutic efficacy of co-administered drugs like Picrorhiza kurroa (Reddy, 2017). This synergistic interaction likely contributed to the observed improvements in hepatic function, lipid profile, and glycemic control in the present case.

Clinically, the patient demonstrated significant improvement in anthropometric parameters, including reduction in body weight, waist circumference, and BMI, indicating a positive impact on obesity. Furthermore, notable improvements in fasting blood glucose, HbA1c, and insulin resistance markers suggest enhanced glucose metabolism. The lipid profile also showed favorable changes, with reductions in total cholesterol, LDL, and triglycerides, along with an increase in HDL levels. These findings are particularly important, as dyslipidemia and insulin resistance are key drivers in the progression of NAFLD.

Improvement in liver enzymes and regression of hepatic steatosis from Grade II to Grade I on ultrasonography further support the hepatoprotective potential of the intervention. These changes may be attributed to the combined effects of reduced hepatic lipid accumulation, improved insulin sensitivity, and decreased inflammatory activity.

In addition to pharmacological intervention, lifestyle modifications including dietary regulation and physical activity played a supportive role in enhancing therapeutic outcomes. The integration of herbal therapy with lifestyle changes reflects a holistic approach, which is a cornerstone of Ayurvedic management.

Overall, the findings of this case are in agreement with existing literature that highlights the efficacy of herbal interventions and polyherbal formulations in the management of metabolic syndrome and NAFLD. The absence of adverse effects during the treatment period further supports the safety and tolerability of the intervention.

However, being a single case study, the findings are limited in terms of generalizability. Further well-designed randomized controlled trials with larger sample sizes are required to validate these results and to elucidate the precise molecular mechanisms underlying the observed therapeutic effects.

6. CONCLUSION

This single case study underscores the significant potential of a combined *Picrorhiza kurroa* and *Piper longum* intervention, coupled with lifestyle modifications, in effectively ameliorating the complex pathological manifestations of high-fat diet-induced insulin resistance, metabolic syndrome, and non-alcoholic fatty liver disease. This robust preliminary evidence necessitates expanded research, including randomized controlled trials, to substantiate these findings across a broader demographic and to elucidate the precise molecular mechanisms underpinning the observed therapeutic effects.

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