

## Abstract

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# Kawakawa and Its Antidiabetic Effects: A Mechanistic Approach

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Type 2 diabetes mellitus (T2DM) is a major disease worldwide, causing significant mortality and morbidity. Currently, in Aotearoa, New Zealand, there is a high prevalence of T2DM, with a disproportionate impact on Māori and Pacific populations<sup>(1)</sup>. Moreover, it has been predicted that the prevalence will continually increase. Research has shown that insulin resistance (IR) has been reported to play a critical role in the development of T2DM and other related cardiometabolic diseases<sup>(2)</sup>. Therefore, managing IR is crucial to reducing the development of T2DM. Notably, bioactive compounds in various diets are known to modify the risk of T2DM by regulating IR. Among such dietary compounds include kawakawa (*Piper excelsum*), an indigenous species used by Māori in traditional medicine (Rongoā). Kawakawa is shown to contain several bioactive compounds that are shown to have insulin-sensitising effects. Research by our group has recently shown kawakawa to have potential anti-diabetic and anti-inflammatory effects in healthy human volunteers<sup>(3,4)</sup>. However, how Kawakawa exerts these effects on insulin signalling and glucose uptake remains unknown. We hypothesise that kawakawa will enhance the glucose uptake in the treated cells and will differentially regulate key genes involved in insulin signalling pathways, including GLUT2, IRS-1, PPAR-γ, and PI3K/Akt, across various tissues. To test our hypothesis, we aim to investigate the mechanistic action of kawakawa extract on insulin signalling pathways in different cell models from metabolically active organs. We will use the same kawakawa powder sample shown to improve postprandial insulin in a healthy population. Cell models representing different insulin-responsive organs: liver (HepG2), skeletal muscle (L6-GLUT4myc), pancreas (MIN6), and adipose (3T3-L1) will be used. The cells will be treated with different doses of kawakawa extract, and glucose uptake will be measured. Key signalling pathways, including GLUT2, IRS-1, PPAR-γ, and PI3K/Akt, will be monitored using western blot and quantitative polymerase chain reaction (qPCR) analysis. The findings of this study have the potential to identify key targets of kawakawa action on insulin signalling in metabolically active organs. These outcomes will inform future research with kawakawa in clinical settings in people with cardiometabolic diseases such as T2DM and can form the basis for developing a dietary intervention for individuals at risk of these diseases. Additionally, Rongoā is an acceptable intervention by Māori, integrating this knowledge with evidence-based scientific interventions would aid in creating a holistic health paradigm that resonates within Māori communities.

**Keywords:** Kawakawa; insulin resistance; T2DM; genes

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## References

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