

## Abstract

In Africa, non-communicable diseases such as diabetes mellitus have been generally neglected. This problem has worsened over the years owing to continuous threats from infectious diseases such as HIV/AIDS, tuberculosis and malaria. Despite this, statistics have shown that by 2030, the African region will have the highest proportional increase in diabetes prevalence. Over 80% of all diabetic deaths occur in developing countries probably not only due to poor equity of access to medication but also due to limited efficacy and side effects associated with the commonly available anti-diabetic agents. Therefore, this creates the desperate need for the development of new anti-diabetic agents that are more efficacious and can be sourced from within the continent.

With oxidative stress as a suggested mechanism underlying the cause of diabetes mellitus and diabetic complications, the discovery of natural anti-oxidants that prevent free radical mediated damage is important for developing new treatment strategies. Marine algae have been identified as good sources for natural anti-oxidants. Unfortunately, very few studies have embarked on the discovery of marine-derived anti-oxidant compounds with potential anti-diabetic activity.

In this project, we investigated the potential anti-oxidant activity of the South African endemic algae *Stypopodium multipartitum*, *Dictyopterus ligulata*, *Cystophora fibriosa*, *Bifurcariopsis capensis*, *Sargassum* sp. and *Sargassum heterophyllum*. From these studies, *Sargassum heterophyllum* yielded prenylated compounds, the main compound being sargahydroquinoic acid (**3.6**) and the carotenoid metabolite fucoxanthin (**3.8**), which are in part responsible for the radical scavenging activity of the crude extract. Sargahydroquinoic acid (**3.6**) and fucoxanthin (**3.8**) also exhibited significant anti-inflammatory activity. Sargaquinoic acid (**3.1**), sargachromenoic acid (**3.9**) and sarganaphthoquinoic acid (**3.10**) were then semi-synthesized from sargahydroquinoic acid (**3.6**) and their *in-vitro* cytotoxicity profiles evaluated using Chang Liver, HT-29, Caco-2 and 3T3-L1 cell lines prior to antidiabetic

testing. From the semi-synthetic derivatives, sargachromenoic acid (**3.9**) exhibited the most potent anti-oxidant activity ( $IC_{50} = 6.99 \mu\text{g/mL}$ ). After the evaluation of antidiabetic activity using 3T3-L1 preadipocyte differentiation, sarganaphthoquinoic acid (**3.10**) showed the most potent insulinomimetic activity at  $1.19 \mu\text{M}$  by inducing a PPAR $\gamma$  response similar to that of rosiglitazone at  $1 \mu\text{M}$ .