Skin cancer has become an international epidemic with an alarming incidence rate which has steadily increased over the past few decades. Conventional treatment for skin cancer has got significant side effects with the possibility of relapse and a vastly decreased quality of life. The most desirable approach to treat skin cancer would be to identify the molecular signals that trigger terminal differentiation and thereby enforcing the cells towards cell death. A recently discovered caspase (caspase-14) is found to be essential for normal skin development which is expressed suprabasally in terminally differentiating human keratinocytes. Caspase-14 is non-apoptotic in nature and mostly involved in terminal differentiation of keratinocytes. In keratinocytes, terminal differentiation is followed by the initiation of specialized apoptosis, which resembles the features like loss of nuclei as in conventional apoptosis, but differs from the programmed cell death phenomenon by resisting cellular degradation and finally taking part in the cornification process. However, declining levels of caspase-14 which often seen in skin cancer cells, has been correlated with the diminished magnitude of terminal differentiation in human keratinocytes warranting a thorough examination of its involvement in cell death mechanisms. Hence, the present study investigated the properties of plant compounds (Betulinic acid, Oleanolic acid, Parthenolide, Luteolin, and Vitamin D₃) for their potential to induce caspase-14 in immortalized human keratinocytes (HaCaT) and melanoma cells (A375). The selected compounds were critically analysed for their potentials to induce caspase-14-mediated terminal differentiation in skin cancer cells viz. antioxidant, cytotoxicity, cell cycle arrest, apoptotic and caspase-14 expression assays. Among the compounds scrutinized, luteolin (LUT), a flavonoid exerted significant (p<0.05) potential in inducing caspase-14 expression, both at the protein and mRNA levels in HaCaT cells when compared to other compounds. LUT also showed an elevated potential than vitamin D₃ (positive control) to trigger caspase-14 expression. The qualitative RT-PCR analysis for the expression of human involucrin, a marker gene for terminal differentiation, further confirmed the effect of LUT to induce caspase-14-mediated terminal differentiation. For the first time, these results substantiate the in vitro potency of LUT to elicit the expression of caspase-14 thereby inducing terminal differentiation in HaCaT cells and hence might serve as an effective agent in skin cancer therapy.