CHAPTER V

GENERAL DISCUSSION AND CONCLUSION

The polyphenols used in this study including Siamois® red wine (SRPE), mamoa wood extracts (MPE) and Siamois® (the mixture 1:1 between SRPE and MPE) stimulated normal myocyte cell growth while doxorubicin completely inhibited. Contrary to normal cells, the polyphenols inhibited cell growth against 5 cancer cell lines including MDA-MB-435, K562, K562/*adr*, GLC4 and GLC4/*adr* cells. In particular, those polyphenols extracted exhibited cytotoxic activities in drug-resistant sublines such as K562/*adr* with overexpression of P-glycoprotein and GLC4/*adr* with overexpression MRP1 protein to their corresponding parental cells. This suggested that the polyphenols stimulated collateral sensitivity of MDR cell.

The results also showed that polyphenols provided an induction of apoptosis of cancer cells, their action on cancer cell can be described as "assisted suicide".

In order to get further insight in to the mechanism of the polyphenols mediated apoptosis-inducing activities in cancer cells. Quercetin, the most abundant compound found in our polyphenol extracts were selected to study its effects on mitochondrial membrane potential ($\Delta\Psi_m$) change as well as its ability to induce apoptosis, against K562 and K562/*adr* cell. Quercetin induced an increase followed by a decrease in $|\Delta\Psi_m|$ value depending on its concentration. A decrease in the $|\Delta\Psi_m|$ value provoked a releasing of cytochrome c to cytoplasm, triggering caspase-9 processing; this signified that polyphenols mediated an induction of apoptosis at the mitochondrial level.

Our results obtained from optical imaging also confirmed that the polyphenols also affect the mitochondrial function in normal myocytes; however without any cellular damage, but it stimulated myocyte cell growth. This is strong evidence suggesting that the physical and chemical environments of mitochondria might be much different in normal myocyte and cancer cell, particularly MDR cells.

The research on potential use of polyphenols for cancer treatment was extended from cell culture to cancerous nude mice. The invasive estrogen-receptor negative MDA-MB-435 cells xenografted in athymic nude mice were used as *in vivo* model for studying cancer cell response to the polyphenol by using molecular imaging technique, the ^{99m}Tc-hynic-Annexin V scintgraphic and histochemical technique.

The double IC_{50} value of the polyphenol exhibited an induction of apoptosis only in tumor tissue. There was no normal tissue damage, particularly the liver. It is the first time that the antiproliferative and apoptosis-inducing effects of the polyphenols on MDA-MB-435 cell *in vitro* were effectively extrapolated to the *in vivo* situation.

The overall results of this study demonstrated that the polyphenol extracts derived from Siamois® red wine (SRPE), mamoa wood extracts (MPE) and Siamois® could be considered as non-toxic compounds; as a matter of fact it looks as if these polyphenols have very few side effects.

THE PROSPECTIVES OF STUDY

To use the Siamois® polyphenols as nutrition-based for prevention and intervention purposes in human, the further studies should be requires including:

1. Clarify active ingredients of Siamois® polyphenols.
2. Investigate the pharmacokinetics and dynamics of Siamois® polyphenols.