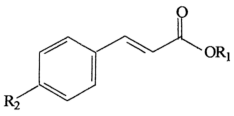
CHAPTER 5

CONCLUSIONS

The chemical study of the CH_2Cl_2 extract of the rhizomes of *Kaempferia galanga* Linn. had afforded three phenolic compounds namely ethyl cinnamate **83**, *p*-methoxycinnamic acid **84** and ethyl *p*-methoxycinnamate **85**. Sixty-two volatile components were also identified from the pet. ether extract using GC-MS.

Comparisons of the ^{1}HNMR data and other spectral data with the literature values assisted in the elucidation of the structures of the phenolics. Figure 5.1 illustrates the proposed biogenetic relationship between these phenolics.



83 $R_1 = CH_2CH_3$, $R_2 = H$

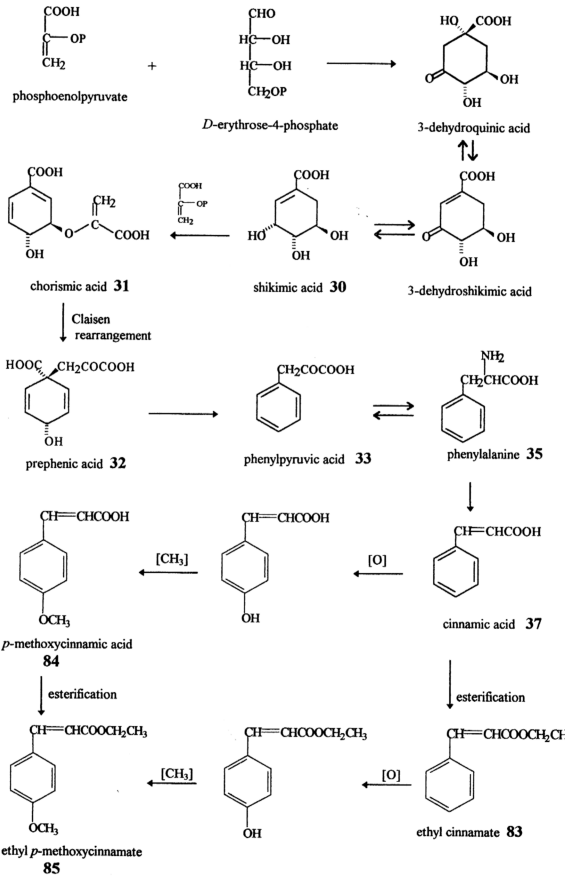
84 $R_1 = H$, $R_2 = OCH_3$

85 $R_1 = CH_2CH_3$, $R_2 = OCH_3$

Preliminary screening using brine shrimp lethality assay and vasorelaxant activity on precontracted rat aorta showed that the CH_2Cl_2 extract possessed antihypertensive activity. Bioassay-guided fractionation of the extract had led to the discovery of the compound responsible for the vasorelaxant activity : ethyl cinnamate. In depth *in vitro* studies of the vasorelaxant activity of this compound against rat thoracic aorta contracted using high K^+ and PE yielded ED_{50} values of 0.30 μg ml^{-1} (≡ 1.70 μM) and 0.38 μg ml^{-1} (≡ 2.16 μM), respectively.

Studies on the mechanisms of vasorelaxant action of ethyl cinnamate and other structurally related compounds suggested that these compounds inhibited both Ca^{2+} influx into the cells via voltage-dependent Ca^{2+} channel and receptor-operated

FIGURE 5.1 THE PROPOSED BIOGENETIC RELATIONSHIP BETWEEN THE PHENOLICS OF *KAEMPFERIA GALANGA* LINN.



Ca^{2+} channels, and Ca^{2+} release from intracellular stores. In addition, the vasorelaxant actions of ethyl cinnamate and cinnamaldehyde **86** might also partially involve the release of endothelium-derived relaxing factor (EDRF) and prostacyclin from the endothelial cells. These findings suggested that ethyl cinnamate, in particular, acted upon various sites causing the relaxation of vascular smooth muscles.

The structure-activity relationship of the vasorelaxant activities of ethyl cinnamate and other structurally similar compounds are shown in table 5.1. All analogs showed lesser or no activity as compared to ethyl cinnamate. The results obtained on the muscle relaxant activity of ethyl cinnamate suggested its potential in the treatment of hypertension. However, before this compound is to be tested clinically, further structure-activity relationship, quantitative structure-activity relationship (QSAR), *in vivo* pharmacological, pharmacokinetic and toxicological studies need to be carried out to establish effective doses and safety profile of the compound.

TABLE 5.1 POSTULATION ON THE STRUCTURE-ACTIVITY RELATIONSHIP OF ETHYL CINNAMATE AND OTHER STRUCTURALLY SIMILAR COMPOUNDS AGAINST THEIR VASORELAXANT ACTIVITIES

Action	Result	Postulation
Increasing the length and bulkiness of side chain of ethyl cinnamate **83** (as in *N*-cinnamalidene-lysin **89** and cinnamyl cinnamate **91**).	Reduction in vasorelaxant activity against contraction induced by both spasmogens.	Bulky or lengthy side chain might introduce steric hindrance to bonding with the receptor at the active site.
Replacing the ethoxy moiety in ethyl cinnamate **83** H atom (as in cinnamaldehyde **86**).	Reduction in vasorelaxant activity.	Hydrogen bonding might be involved in the bonding of ethyl cinnamate to the active site, and a change in the degree of the hydrogen bond might reduce the effectiveness of the bonding.
Substituting the aromatic ring in ethyl cinnamate **83** with CH_3O group at *para* position (as in *p*-methoxycinnamic acid **84** and ethyl *p*-methoxy-cinnamate **85**).	No vasorelaxant activity.	Introduction of an electron-donating group at *para* position of the aromatic ring might change the electron distribution / factor of the ring or might increase the bulkiness of the ring and led to steric hindrance.
Replacing the $-CO_2-$ in ethyl cinnamate **83** with N-containing moiety (as in *N*-cinnamalidene-*p*-fluoroaniline **87** and *N*-cinnamalidene-*p*-methoxyaniline **88**).	Reduction in vasorelaxant activity.	Hydrogen bonding might be involved in the bonding of ethyl cinnamate to the active site, and a change in the degree of the hydrogen bond might reduce the effectiveness of the bonding.