

## List of Abbreviations

% CV	percent coefficient of variation
% F	percent bioavailability
% RE	percent relative error
% RSD	percent relative standard deviation
% w/v	percent weight by volume
% v/v	percent volume by volume
°C	degree Celsius
µg	microgram
µL	microliter
µm	micrometer
µM	micromolar
5-HT	5-hydroxytryptamine
ACC	american college of cardiology
ADMET	absorption, distribution, metabolism, excretion and toxicity
AHA	american heart association
ALT	alanine aminotransferase
AMPK	adenosine monophosphate-activated protein kinase
arb	arbitrary unit
ATP	adenosine triphosphate
AUC	area under curve
BCS	biopharmaceutics classification
BLK	blank
BMI	body mass index
BSA	bovine serum albumin
CE	collision energy
Conc.	concentration
Cl	clearance
C <sub>max</sub>	maximum concentration
CS	calibration standards
CSF	cerebro-spinal fluid
C <sub>ss</sub>	steady state concentration
CXP	collision exit potential
CYP	cytochrome p450 enzymes
Da	dalton
DME	drug metabolising enzyme
DMSO	dimethyl sulphoxide
DP	declustering potential
EDTA	ethylenediaminetetraacetic acid

e.g.	example
ELISA	enzyme-linked immunosorbent assay
EP	entrance potential
ESI	electro spray ionisation
eV	electron volt
FA	flufenamic acid
FC	frozen condition
FDA	food and drug administration
FT-C	freeze thaw-cycle
g	gram
GA	glycyrrhetic acid
GCE	<i>Garcinia cambogia</i> extract
GC-MS	gas chromatography-mass spectrometry
GLP	glucagon like peptide
GLZ	glycyrrhizin
h	hour
HCA	hydroxycitric acid
HCl	hydrochloric acid
HETP	height equivalent to theoretical plates
HFD	high fat diet
HILIC	hydrophilic interaction liquid chromatography
HPLC	high-performance liquid chromatography
HQC	high quality control
HRMS	high resolution mass spectrometer
<i>i.e.</i>	that is
<i>i.p.</i>	intra peritoneal
<i>i.v.</i>	intra venous
IAEC	institutional animal ethics committee
IS	internal standard
IU	international unit
KCl	potassium chloride
Kg/m <sup>2</sup>	kilogram per meter square
KV	kilovolt
L/Kg	litre per kilogram
LC-MS/MS	liquid chromatography with tandem mass spectrometry
LDL	low density lipoprotein
LLE	liquid-liquid extraction
LN%	natural logarithmic of the percentage
LLOQ	lower limit of quantitation
LLOQQC	lower limit of quantification quality control

LQC	low quality control
mg	milligram
mg/kg	milligram per kilogram
mg/mL	milligram per millilitre
min	minute
mL	millilitre
mL/kg	millilitre per kilogram
mM	millimolar
mm	millimeter
MQC	mid quality control
MRM	multiple reaction monitoring
mRNA	messenger ribonucleic acid
MRT	mean residence time
MS	mass spectrometer
ms	millisecond
NADPH	nicotinamide-adenine dinucleotide phosphate
NCD	non-communicable diseases
NCE	new chemical entity
ng/mL	nanogram per millilitre
PBS	phosphate buffer saline
PDA	photodiode array detector
pH	potential of hydrogen
pKa	acid dissociation constant
PK	pharmacokinetic
P-gp	p-glycoprotein
<i>p.o.</i>	per oral
PPAR	peroxisome proliferator activated receptor
ppm	parts per million
<i>psi</i>	pound per square inch
PXR	pregnane-x receptor
QC	quality control
QCN	quercetin
QTE	quetiapine
RL S9	rat liver s9 fraction
RLH	rat liver homogenate
rpm	rotation per minute
SD	standard deviation
S/N	signal to noise
SPE	solid phase extraction
TCA	trichloroacetic acid

TG	triglycerides
$t_{1/2}$	half life
$T_{max}$	time to reach maximum concentration
TNF	tumor necrotic factor
TOS	the obesity society
UCP	uncoupling protein
UGT	udp -glucuronosyltransferase
ULOQ	upper limit of quantitation
ULOQWS	upper limit of quantitation of working solution
UPLC	ultra-performance liquid chromatography
USA	united states of America
USFDA	united states food and drug administration
UV	ultra violet
V	volts
$V_d$	volume of distribution
WAT	white adipose tissue
WHR	waist-hip ratio
WHO	world health organization

## List of Figures

Figure	Title	Page
1.1	Prevalence of obesity (BMI $\geq 30$ kg/m <sup>2</sup> ) in selected countries from Organisation for Economic Cooperation and Development, OECD 2017	3
1.2	Percentage of adults defined as obese by country in 1975 (Part A) and 2014 (Part B)	4
1.3	Various categories of mechanisms of action of anti-obesity activity by botanicals and their natural products	15
1.4	Radar chart depicting distribution of anti-obesity activity in various botanical parts	16
1.5	Chemical categories of natural products responsible for the anti-obesity activity	17
2.1	Known interactions of commonly used herbs with drugs from different therapeutic classes	28
2.2	Known interactions (both activation and inhibition) of commonly used herbs with different CYP enzymes	32
3.1	Chemical structures of all the analytes (A,C,D,E,G) and internal standards (B,F)	59
4.1	Predicted (theoretical) mass fragmentation ions of HCA	80
4.2	Predicted (theoretical) mass fragmentation ions of QCN	83
4.3	Predicted (theoretical) mass fragmentation ions of GLZ (A) and GA(B)	90
5.1	Representative chromatograms of A) Blank, B) LLOQ, and C) Internal standard	102
5.2	Plasma concentration-time profile of HCA after administration of HCA ( <i>i.v.</i> and <i>p.o.</i> ) and <i>Garcinia</i> ( <i>p.o.</i> ) in Wistar rats (n=3)	106
5.3	Representative chromatograms of blank injected after ULOQ standard	110
5.4	Plasma concentration-time profile of QCN after administration of QCN ( <i>p.o.</i> ) in Wistar rats (n=3).	116
5.5	Plasma concentration-time profile of GA after administration of GLZ ( <i>p.o.</i> ) in Wistar rats (n=3)	117

**List of Figures (Continued)**

<b>Figure</b>	<b>Title</b>	<b>Page</b>
6.1	Plasma concentration-time profile of QTE after administration of QTE ( <i>p.o.</i> ) alone and along with HCA in Wistar rats (n=6).	125
6.2	Plasma concentration-time profile of QTE after administration of QTE ( <i>i.v.</i> ) alone and along with HCA in Wistar rats (n=6).	126
6.3	Semi-log plot of QTE remaining Vs time (minutes) incubated in RLS9 in the presence and absence of HCA	127
6.4	Plasma concentration-time profile of QTE after administration of QTE ( <i>i.v.</i> and <i>p.o.</i> ) alone and along with QCN ( <i>p.o.</i> ) in Wistar rats	128
6.5	Box and Whisker plots for brain concentration (ng/mL) of QTE after dosing alone and along with QCN	129
6.6	Semi-log plot of QTE remaining Vs. time (minutes) incubated in RLS9 in the presence and absence of QCN	130
6.7	Plasma concentration-time profile of QTE after administration of QTE ( <i>p.o.</i> ) alone and along with GLZ in Wistar rats (n=6).	131
6.8	Box and Whisker plots for brain concentration (ng/mL) of QTE after dosing alone and along with GLZ	132
6.9	Plasma concentration-time profile of QTE after administration of QTE ( <i>i.v.</i> ) alone and along with GLZ in Wistar rats (n=6).	133
6.10	Semi-log plot of QTE remaining Vs. time (minutes) incubated in RLS9 isolated from control rats and rats pre-treated with GLZ	133

## List of Tables

Table	Title	Page
1.1	Summary of BMI based classification for overweight and obesity in different age groups	5
1.2	List of factors influencing the chronic positive energy balance	6
1.3	Botanicals, their parts, family, natural products and plausible mechanism of action of anti-obesity	9-14
2.1	CYP450 with most known interaction potential	33
2.2	Synergistic herb-drug interactions mediated through CYP enzymes	34-35
2.3	Summary of clinical studies conducted on <i>G. cambogia</i> extract and HCA	38-39
2.4	Modulation of transporters by QCN	40
2.5	Induction of CYP3A by GLZ during <i>in vivo</i> studies	42
2.6	Modulation of UGTs by GLZ and GA	42
2.7	Modulation of P-gp by GLZ and GA	43
3.1	Major working parameters for tandem mass-spectrometer method	65
3.2	Study design for the estimation of pharmacokinetic parameters of HCA in Wistar rats	72
3.3	Study design for the estimation of pharmacokinetic parameters of QCN and GLZ in Wistar rats.	73
3.4	Study design for understanding HCA-QTE pharmacokinetic interaction	74
3.5	Study design for understanding QCN-QTE pharmacokinetic interaction	75
3.6	Study design for understanding GLZ-QTE pharmacokinetic interaction	76
4.1	Output of ADMET Predictor <sup>®</sup> for metabolite prediction of HCA	79
4.2	Exact mass (m/z) of the expected metabolites of HCA	80-81
4.3	Metabolite of HCA obtained after incubation in RLS9.	81
4.4	Output of ADMET Predictor <sup>®</sup> for metabolite prediction of QCN	82
4.5	Exact mass (m/z) of the expected metabolites of QCN	84-85
4.6	Metabolites of QCN obtained after incubation in RLS9	85-86
4.7	Output of ADMET Predictor <sup>®</sup> for metabolite prediction of GLZ	88
4.8	Output of ADMET Predictor <sup>®</sup> for metabolite prediction of GA	88-89

...Continued

<b>Table</b>	<b>Title</b>	<b>Page</b>
4.9	Exact mass (m/z) of the expected metabolites of GLZ and GA	90-92
4.10	Metabolites of GA obtained after incubation in RLS9	92
5.1	Representative system suitability data of HCA obtained before injecting the second Precision and Accuracy batch	101
5.2	Calibration curve data for HCA run on five different occasions fitted to linear regression with $1/x^2$ weighing	102
5.3	Precision and accuracy determination of HCA quality control samples in rat plasma	103
5.4	Recovery and matrix effect for HCA in rat plasma at LQC, MQC and HQC levels	104
5.5	Stability data of HCA under different storage conditions	105
5.6	Pharmacokinetic parameters of HCA after administration of HCA ( <i>i.v.</i> and <i>p.o.</i> ) and <i>Garcinia</i> ( <i>p.o.</i> ) in Wistar rats (n=3)	106
5.7	Incurred sample reanalysis of selected samples for HCA	107
5.8	Representative system suitability of QCN, GLZ, GA, and QTE data obtained before injecting first precision and accuracy batch	109
5.9	Calibration curve data for QCN, GLZ, GA and QTE run on five different occasions fitted to linear regression with $1/x^2$ weighing	111
5.10	Precision and accuracy determination of QCN, GLZ, GA and QTE quality control samples in rat plasma	112
5.11	Recovery and matrix effect for QCN, GLZ, GA and QTE in rat plasma at LQC, MQC and HQC levels	113
5.12	Stability of QCN, GLZ, GA and QTE under storage conditions	114-115
5.13	Pharmacokinetic parameters of QCN after administration of QCN ( <i>p.o.</i> ) in Wistar rats (n=3)	116
5.14	Incurred sample reanalysis of selected samples for QCN	116
5.15	Pharmacokinetic parameters of GA after administration of GLZ ( <i>p.o.</i> ) in Wistar rats (n=3)	117



...Continued

<b>Table</b>	<b>Title</b>	<b>Page</b>
5.16	Incurred sample reanalysis of selected samples for GA after dosing GLZ	118
6.1	Pharmacokinetic parameters of QTE in Wistar rats (n=6) following <i>p.o.</i> administration of QTE alone and QTE along with HCA	125
6.2	Pharmacokinetic parameters of QTE in Wistar rats (n=6) following <i>i.v.</i> administration of QTE alone and QTE along with HCA	126
6.3	Pharmacokinetic parameters of QTE in Wistar rats (n=6) following <i>p.o.</i> administration of QTE alone and QTE along with QCN	129
6.4	Pharmacokinetic parameters of QTE in Wistar rats (n=6) following <i>i.v.</i> administration of QTE alone and QTE along with QCN	130
6.5	Pharmacokinetic parameters of QTE in Wistar rats (n=6) following <i>p.o.</i> administration of QTE alone and QTE along with GLZ	131
6.6	Pharmacokinetic parameters of QTE in Wistar rats (n=6) following <i>i.v.</i> administration of QTE alone and QTE along with GLZ	132

### List of Formula

<b>Formula</b>	<b>Title</b>	<b>Page</b>
Formula 3.1	Percentage Recovery	69
Formula 3.2	Percentage Stability	69
Formula 3.3	Incurred Sample Re-analysis	72
Formula 3.4	Absolute bioavailability	73

## List of Symbols

$\alpha$	alpha
$\approx$	approximate
$\beta$	beta
$\downarrow$	decrease
$>$	greater than
$\geq$	greater than or equal to
$\uparrow$	increase
$<$	less than
$\leq$	less than or equal to
$\%$	percent
$\pm$	plus-minus
$\text{\textcircled{R}}$	registered