New Approach to CWP

Michael McCawley, Ph.D.
School of Public Health

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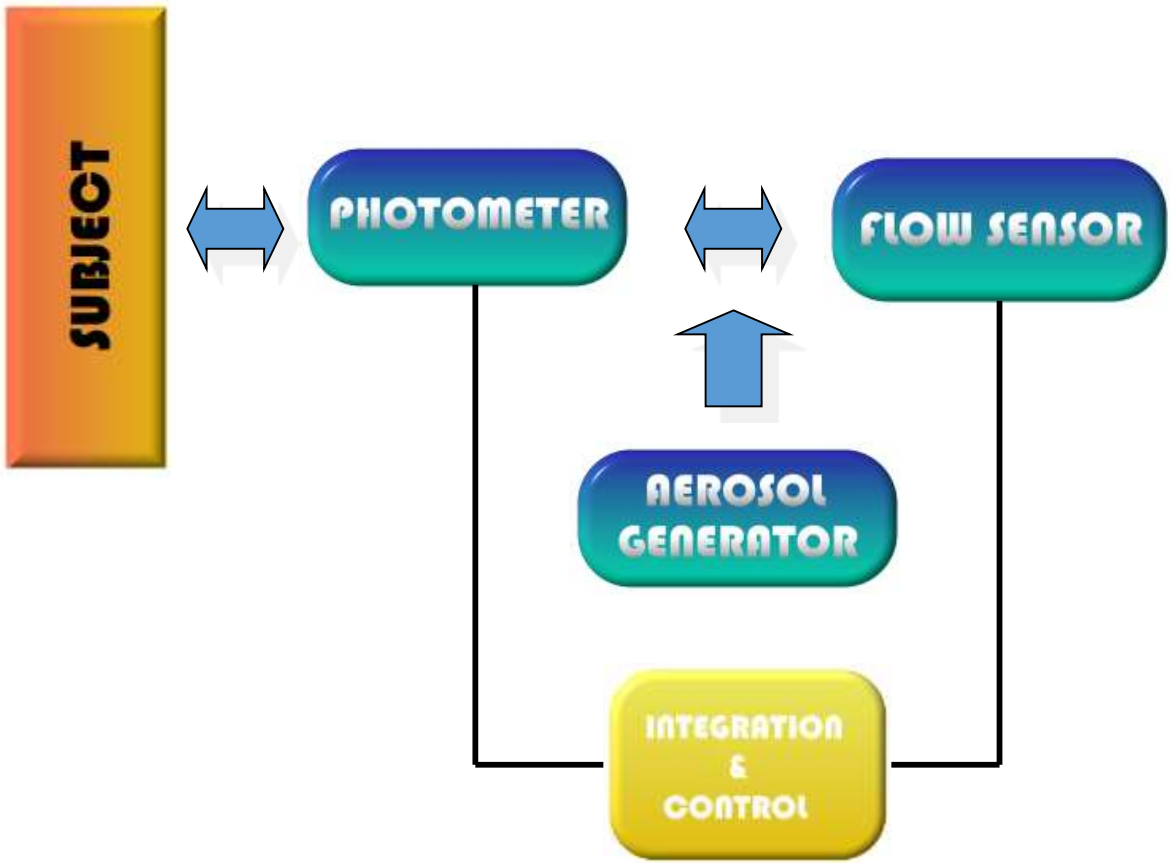
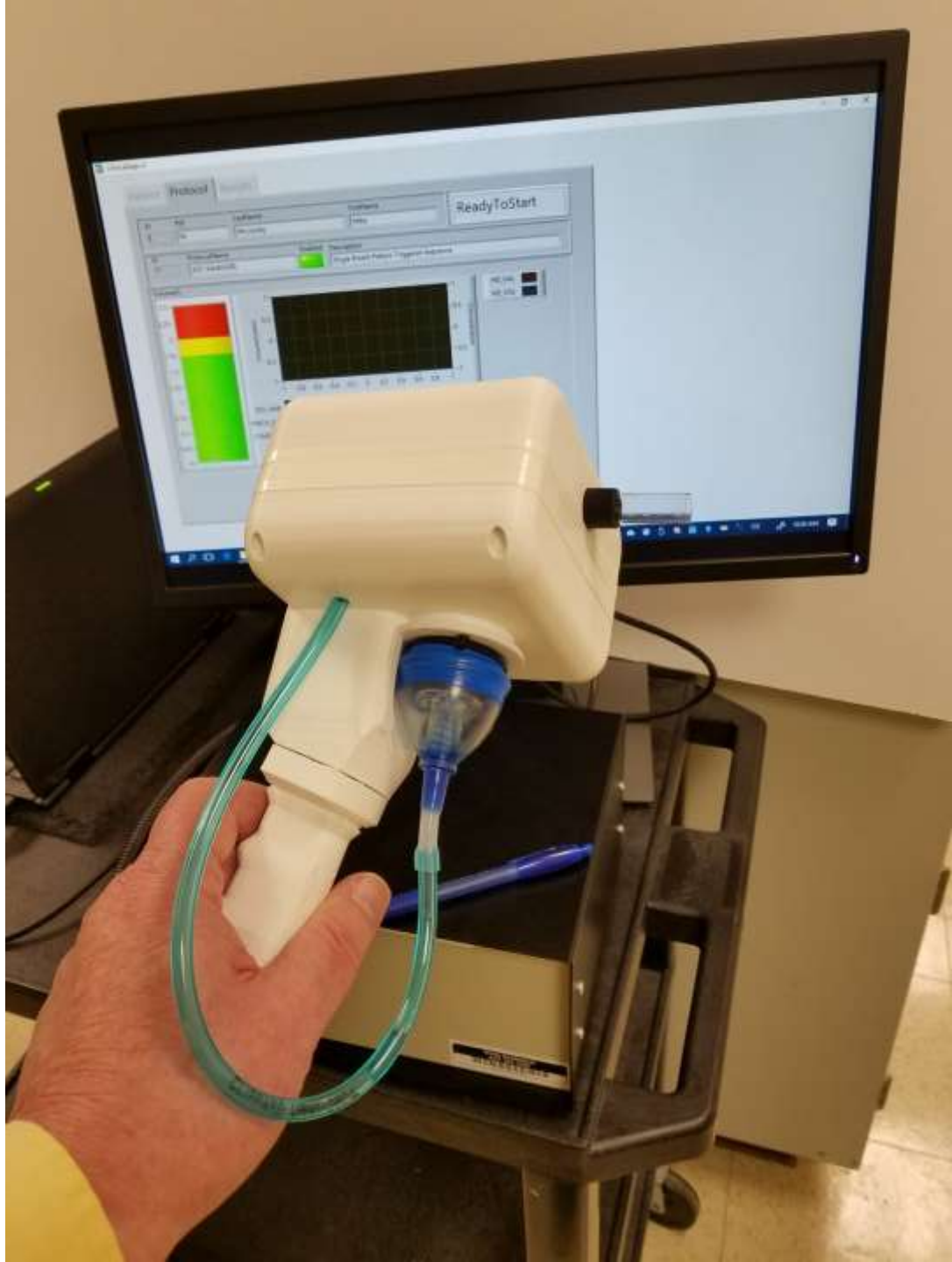
New Approach

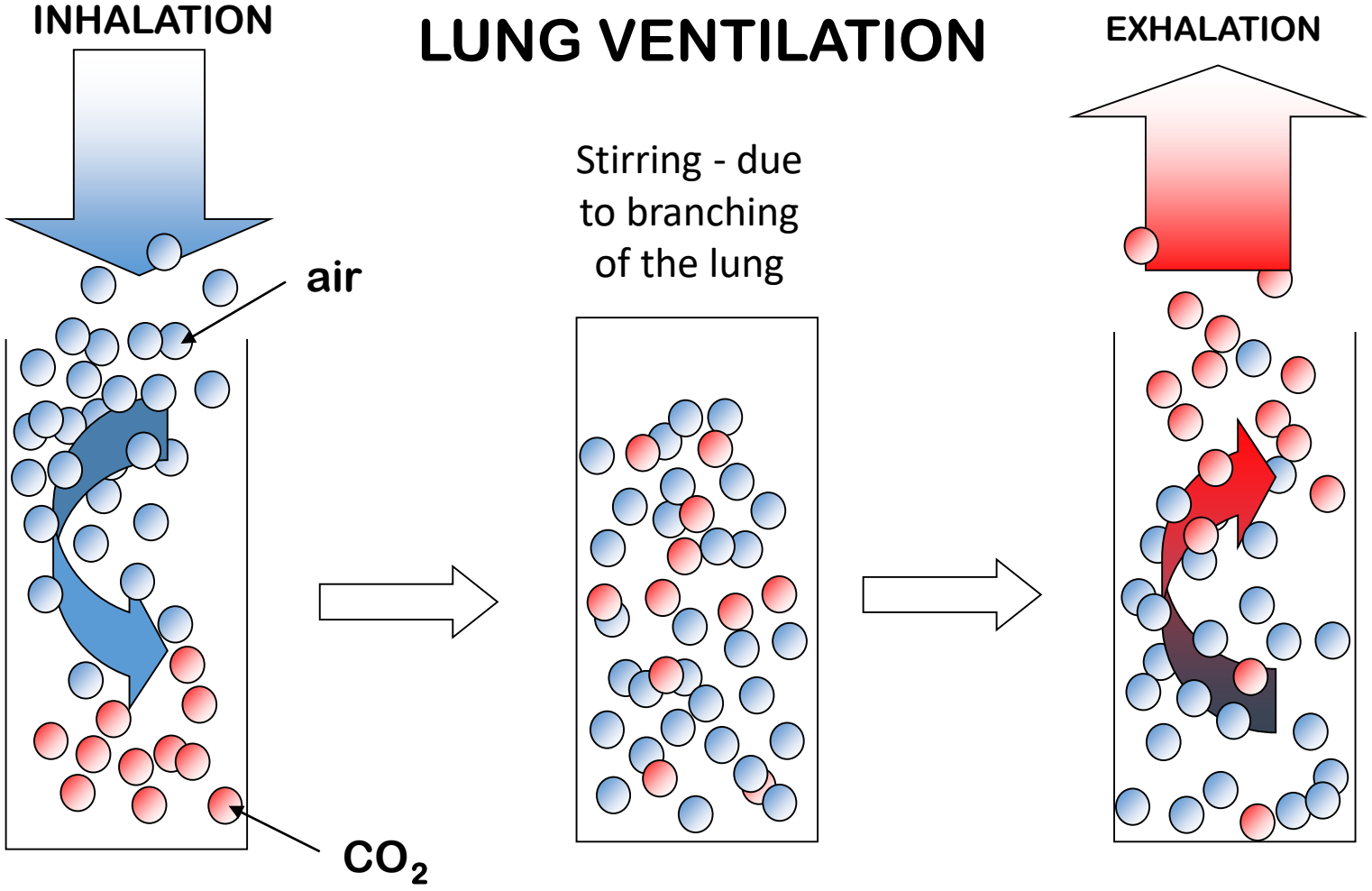
- Better Pulmonary Function = Better Surveillance = Earlier Detection
    - Easier to do
    - Faster
    - More sensitive
- Better Treatment to Slow Progression - Dihydroberberine
    - Anti-inflammatory
    - Calcium channel blocker
    - Supplement

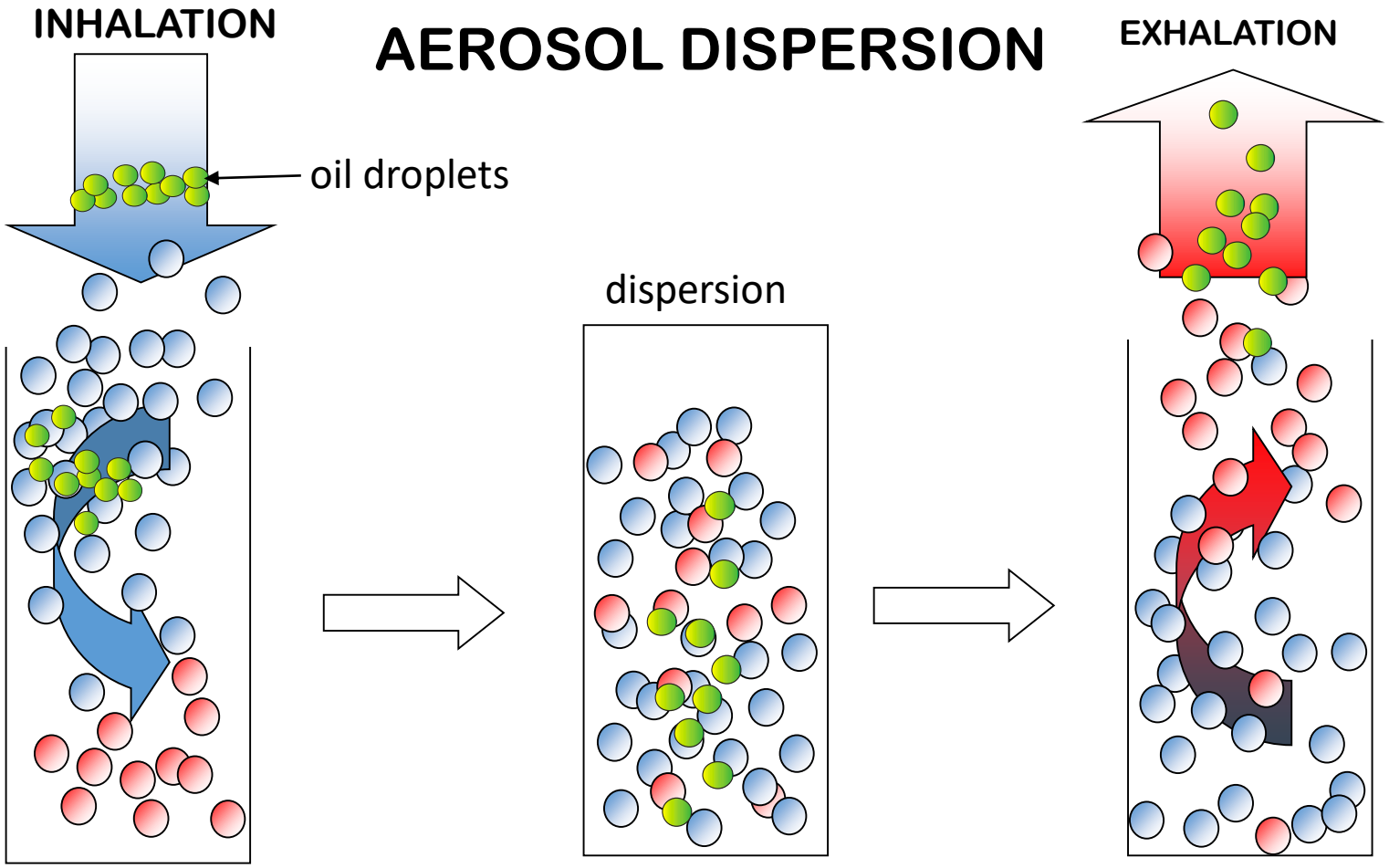
Aerosol Spirometry


SUBJECT
PHOTOMETER
FLOW SENSOR
AEROSOL GENERATOR
INTEGRATION & CONTROL

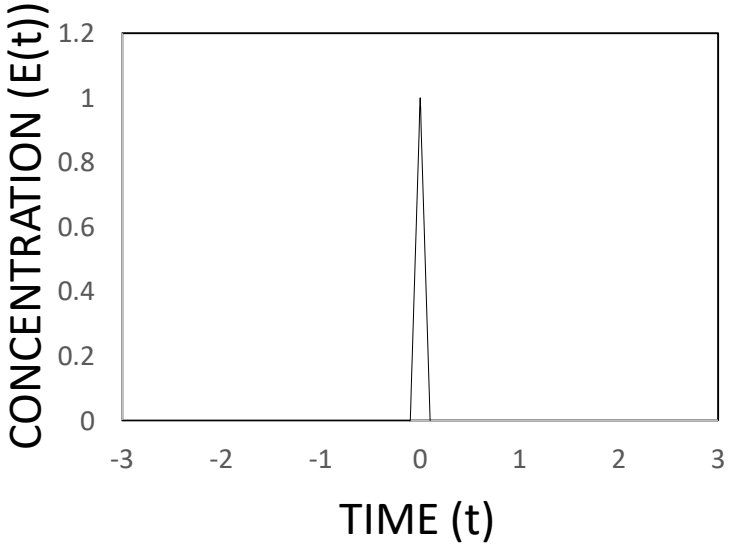

ReadyToStart

LUNG VENTILATION

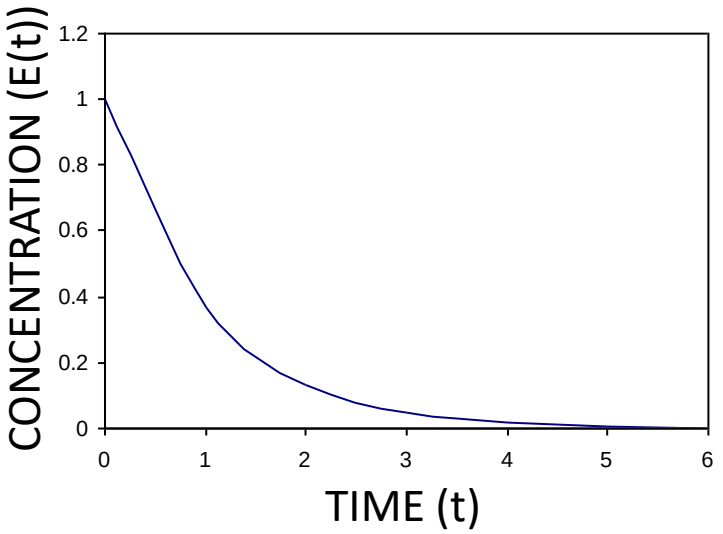



INHALATION
AEROSOL DISPERSION
EXHALATION
oil droplets
dispersion

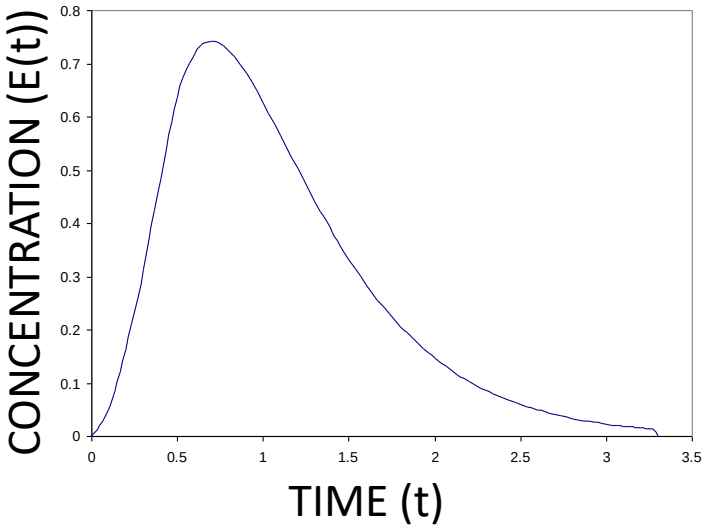
INPUT



1 Chamber

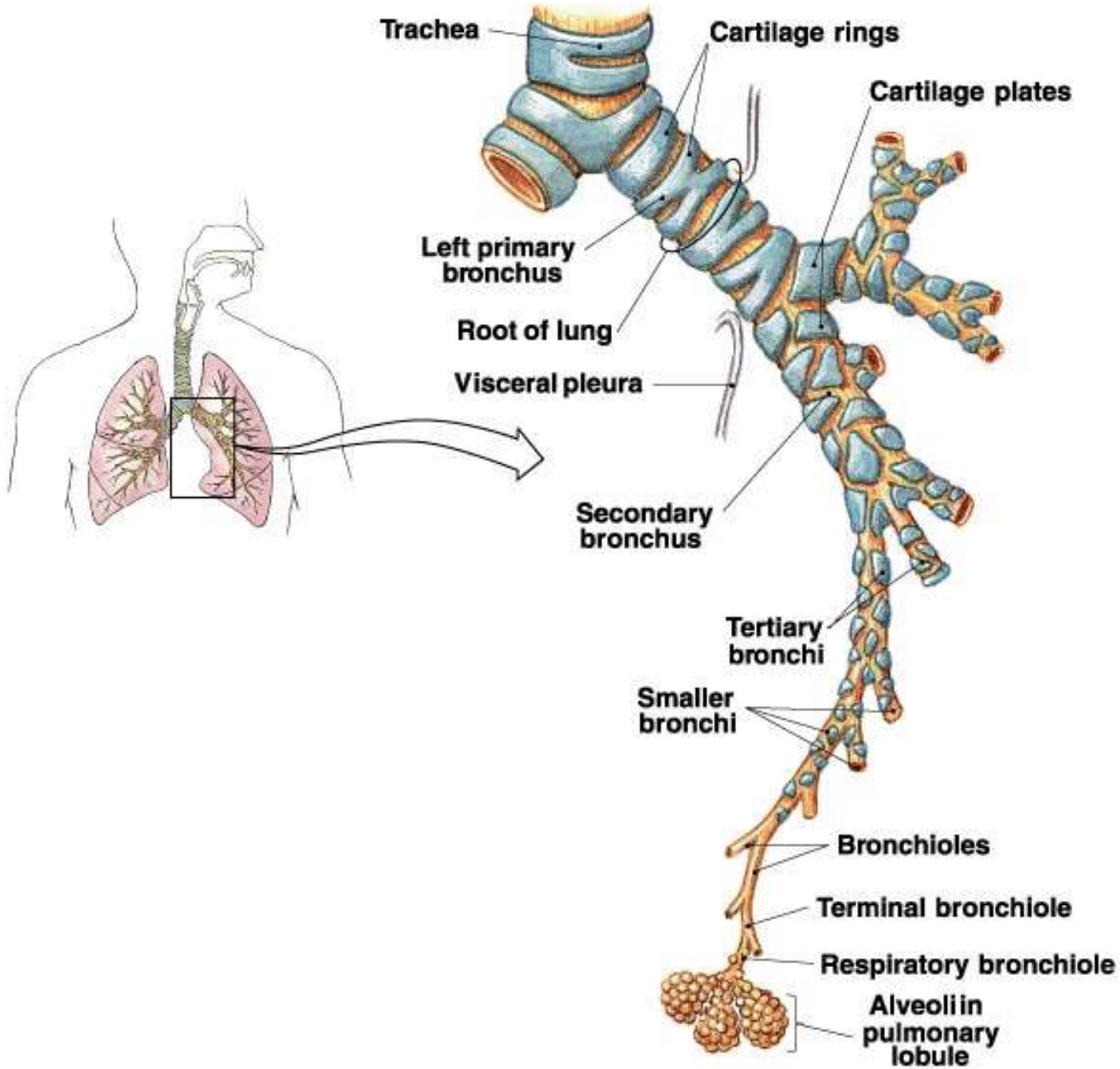


"p" Chambers in series



V_a (apparent volume) = V/β

$$E(t)= \frac{\beta\,(\beta p)^{p}}{t^{p}\,\Gamma(p)}\; t^{p-1}\; e^{-p\beta t}$$

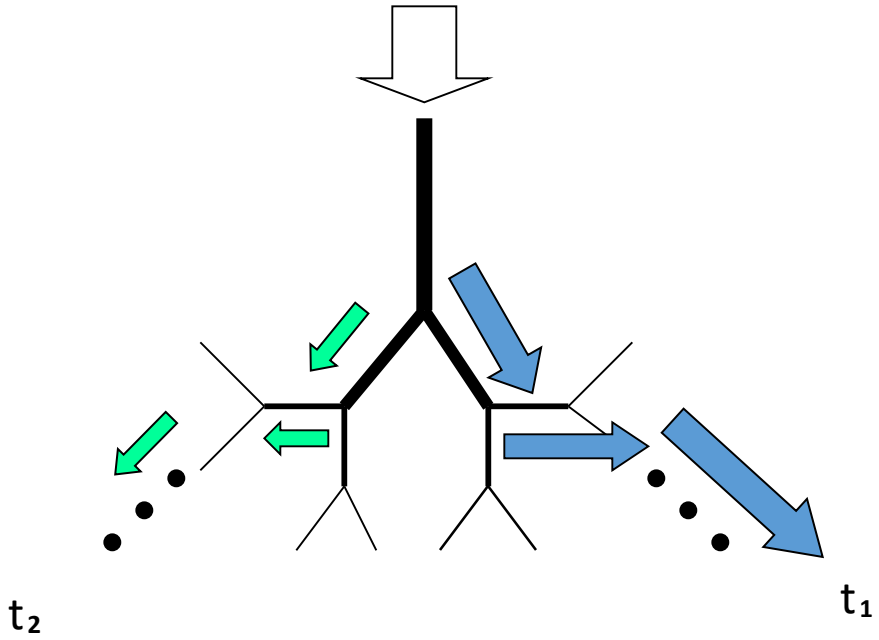


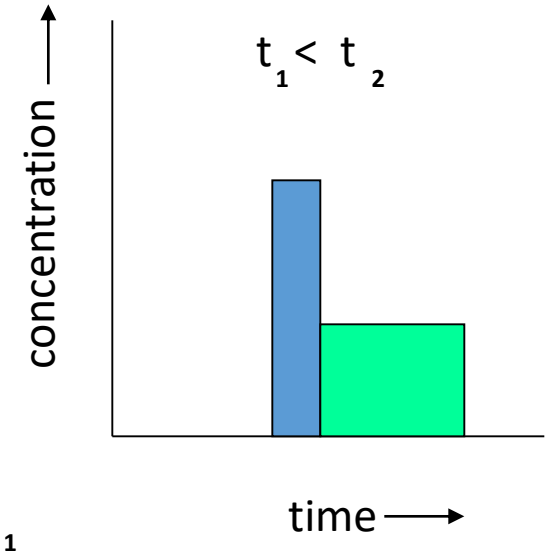
RESISTANCE

COMPLIANCE

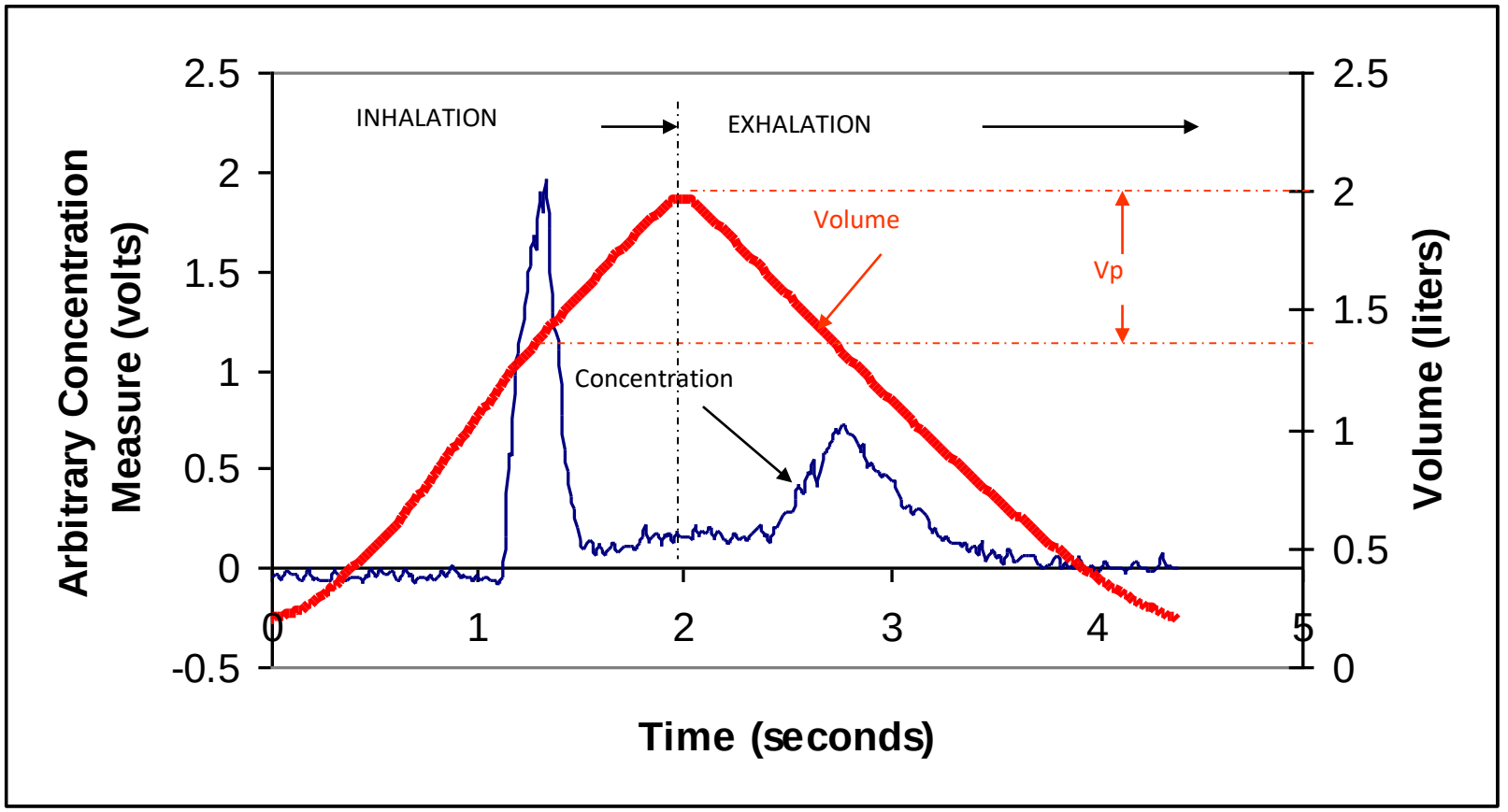
$$\frac{\cancel{\text{Pressure}}\ \text{Time}}{\cancel{\text{Volume}}} * \frac{\cancel{\text{Volume}}}{\cancel{\text{Pressure}}}$$

RESISTANCE * COMPLIANCE = TIME

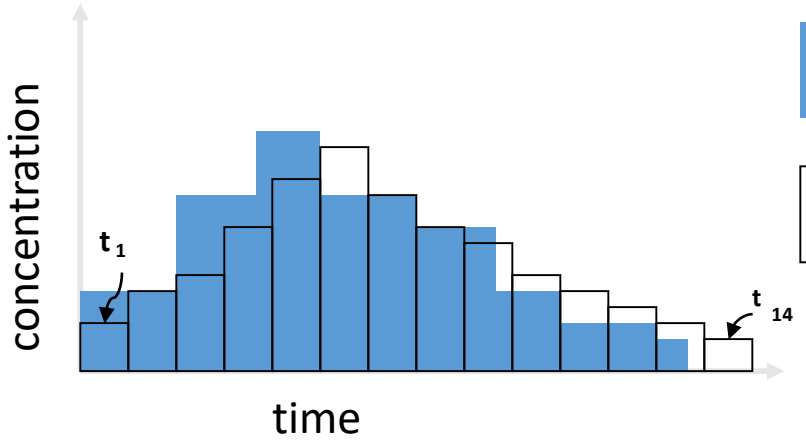




OUTPUT


INHALATION
EXHALATION
Volume
Vp
Concentration
Arbitrary Concentration Measure (volts)
Volume (liters)
Time (seconds)
2.5
2
1.5
1
0.5
0
-0.5
0
1
2
3
4
5

Homogeneity of Ventilation

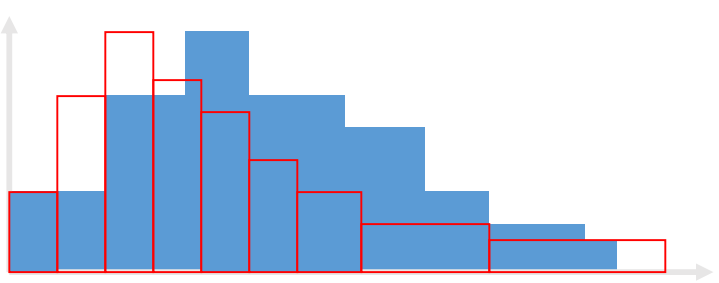


Asymptomatic

COPD

β < 1 (Compliance dominated)

In COPD, particles come out over a longer time and later on average.

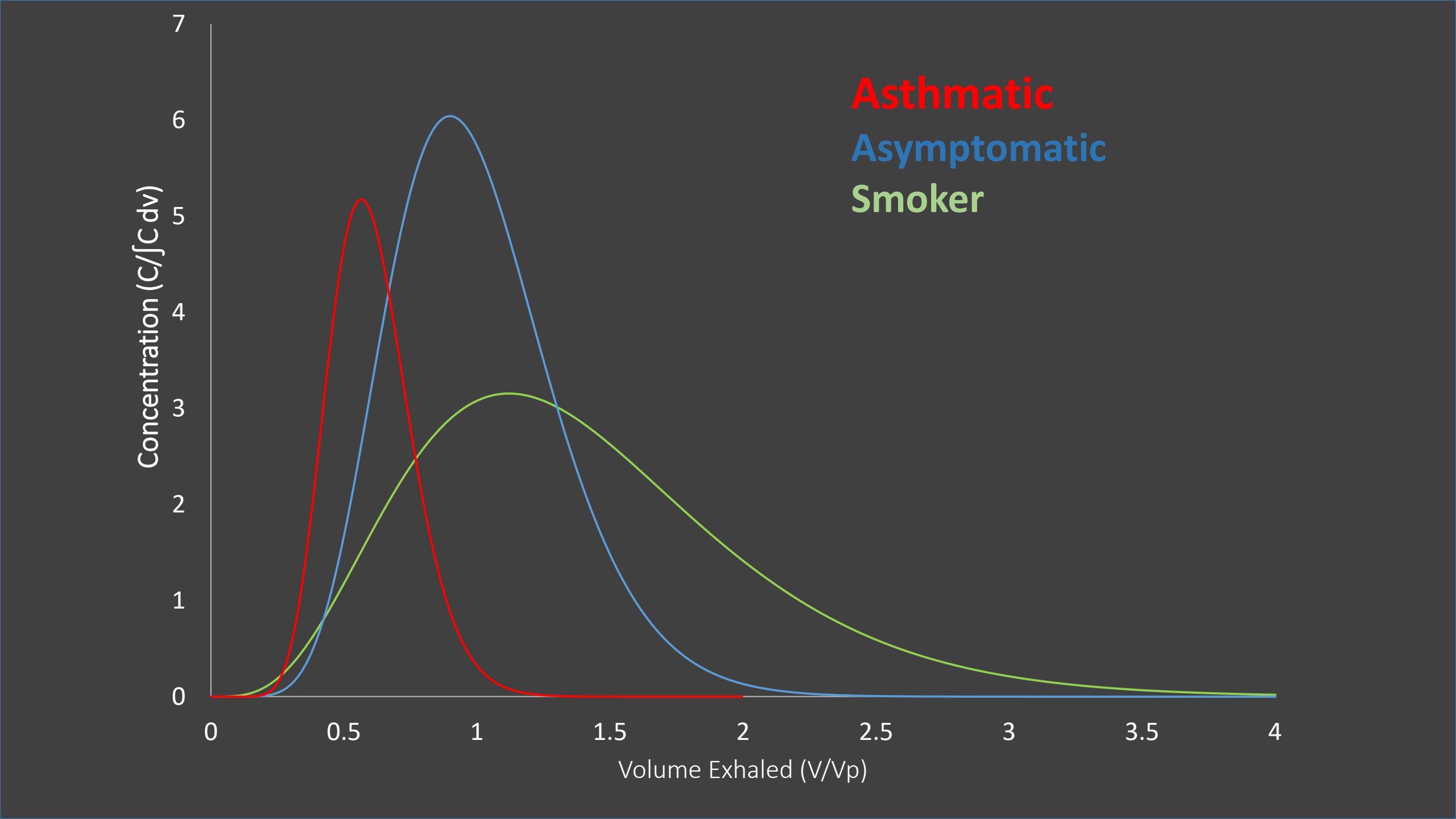


Asymptomatic

Asthmatic

B > 1 (Resistance dominated)

In Asthma, particles come out over a shorter time, and earlier on average.


Asthmatic
Asymptomatic
Smoker
Concentration (C/∫C dv)
7
6
5
4
3
2
1
0
0
0.5
1
1.5
2
2.5
3
3.5
4
Volume Exhaled (V/Vp)

1. Aerosol Spirometry is at least as sensitive as spirometry in detecting known alterations in the lung - Blanchard, 1996.

2. Aerosol Spirometry is simple to administer and patients can successfully perform the maneuver - Blanchard, 1996.

3. Values for pulmonary function derived from Aerosol Spirometry are independent of the tidal volume used in testing- Brown et al., 1995.

4. Values for pulmonary function derived from Aerosol Spirometry are independent of the breathing rate used in testing - McCawley and Lippmann, 1988; Darquenne et al., 1997.

5. For pulmonary function changes in small airways Aerosol Spirometry is more sensitive than standard spirometry - McCawley and Lippmann, 1988; Brand et al., 1994; Anderson et al., 1994.

6. Lung volume differences, even as much as those between children and adults, have no effect on the values derived from Aerosol Spirometry - Schulz et al., 1994.

7. Aerosol Spirometry is at least as sensitive as spirometry in detecting alterations in lung function due to asthma - Schulz et al., 1995.

8.In carbachol induced bronchoconstriction Aerosol Spirometry results correlated with changes in airway conductance - Siekmeier et al., 1994.

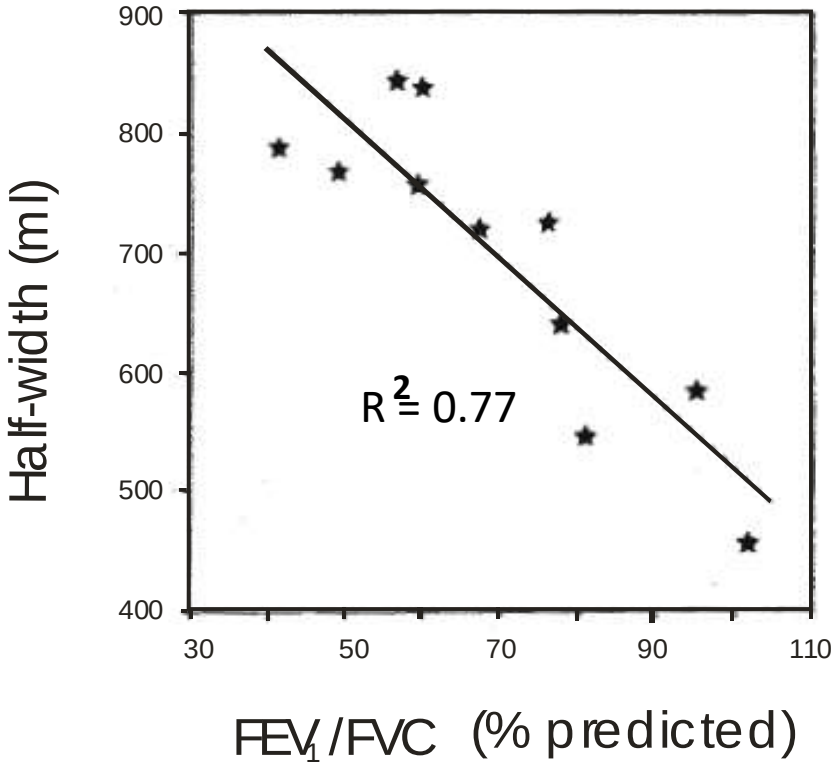
9. Aerosol Spirometry is at least as sensitive as specific airway conductance in detecting methacholine induced airway constriction in normal subjects and exhibits less intrasubject variability - Hardy et al., 1998.

10. Aerosol Spirometry is a powerful tool in the differential diagnosis of chronic obstructive lung disease with higher sensitivity and specificity than conventional lung function parameters for separating patients with chronic bronchitis from those with chronic bronchitis and emphysema-Kohlhäufl, et al., 1998.

11. Aerosol Spirometry can distinguish morphometric changes caused by emphysema from those caused by fibrosis - Brand et al., 1999.

12. Aerosol Spirometry values are correlated with spirometry values in patients with cystic fibrosis patients and changes in proportion to the change in severity of the obstruction - Anderson et al., 1989; Brown et al., 1998.

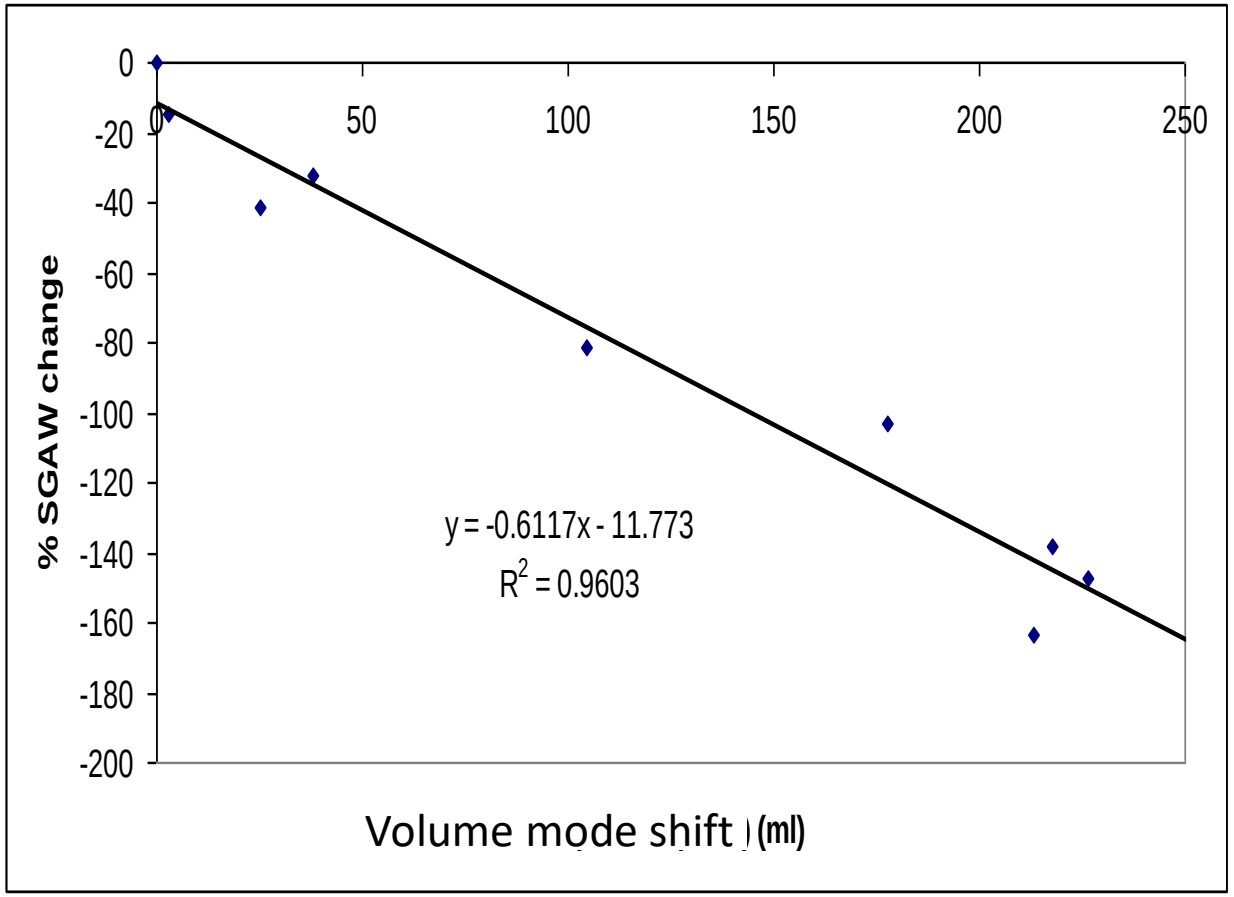
SPIROMETRY



DISPERSION IN CF PATIENTS

Anderson, P.J. et al.
Effect of cystic fibrosis on inhaled aerosol boluses.
Am. Rev. Respir. Dis. 140:1317-1324 (1989)

PLETHYSMOGRAPHY



DISPERSION WITH METHACHOLINE

Hardy, K.G. et al. Sensitivity of aerosol bolus behavior to methacholine induced bronchoconstriction.
Chest 114:404-410.(1998)

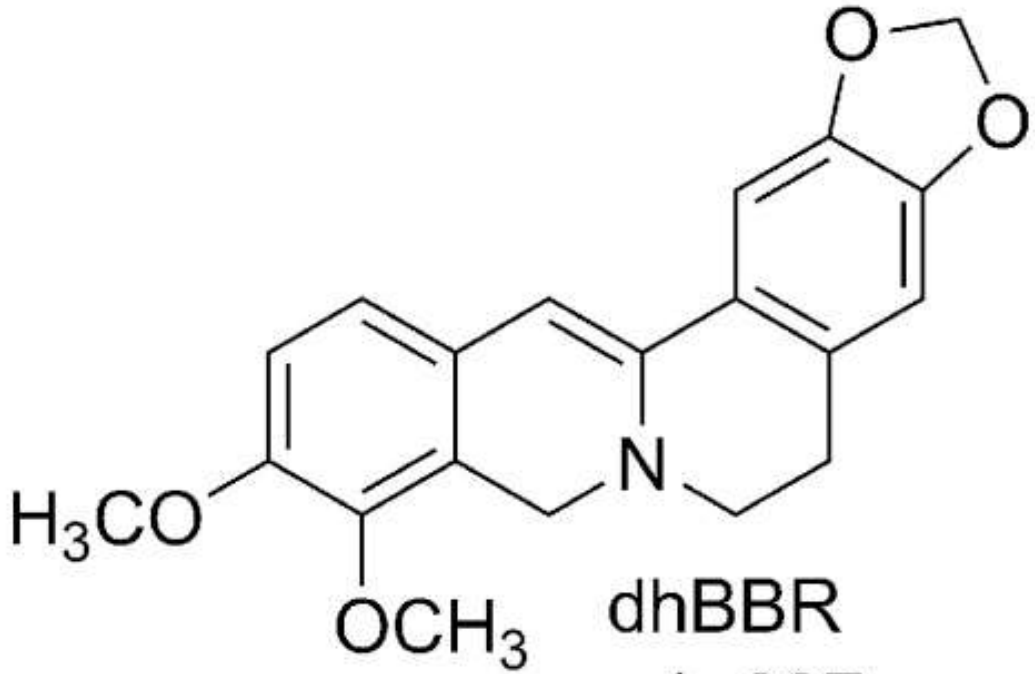
Correlation of Aerosol Spirometry to PFT Values

Independent Variable	Dependent Variables	Number of Subjects	r^2
FEV1	β/p/Stdev	6	0.77
Raw	p	5	0.91
Raw	β /p/HW	5	0.99
SVC	β /p/V_p	5	0.99
IC	β /p/ V_p	5	0.84
TLC	β /p/ V_p	5	0.98
TGV	β /p/ V_p	5	0.96

McCawley et al. 2019

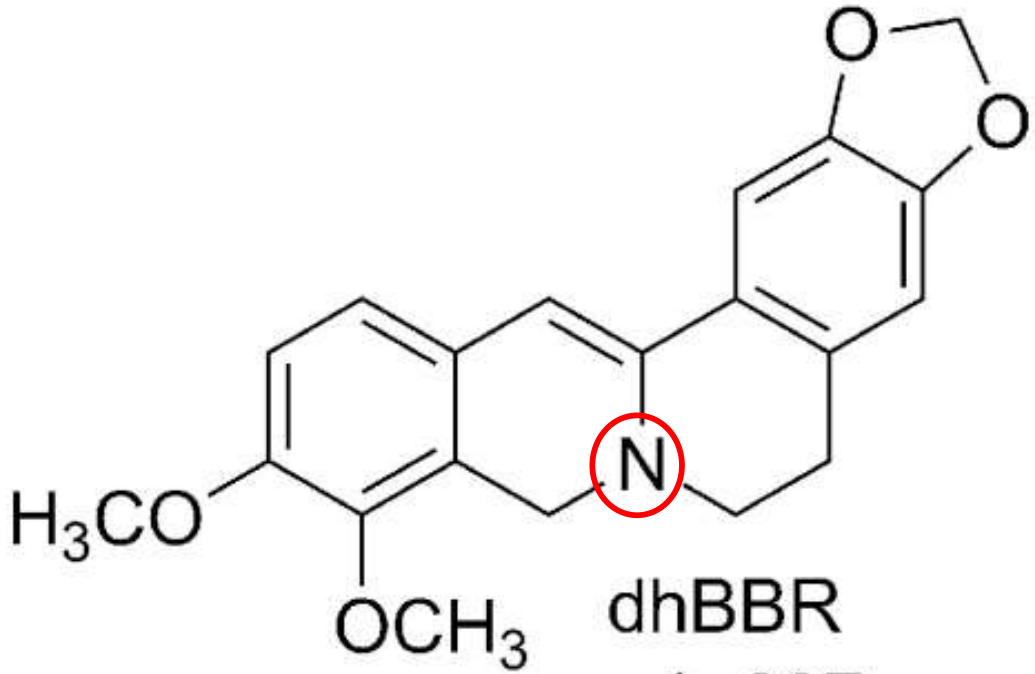
DEMO

Dihydroberberine



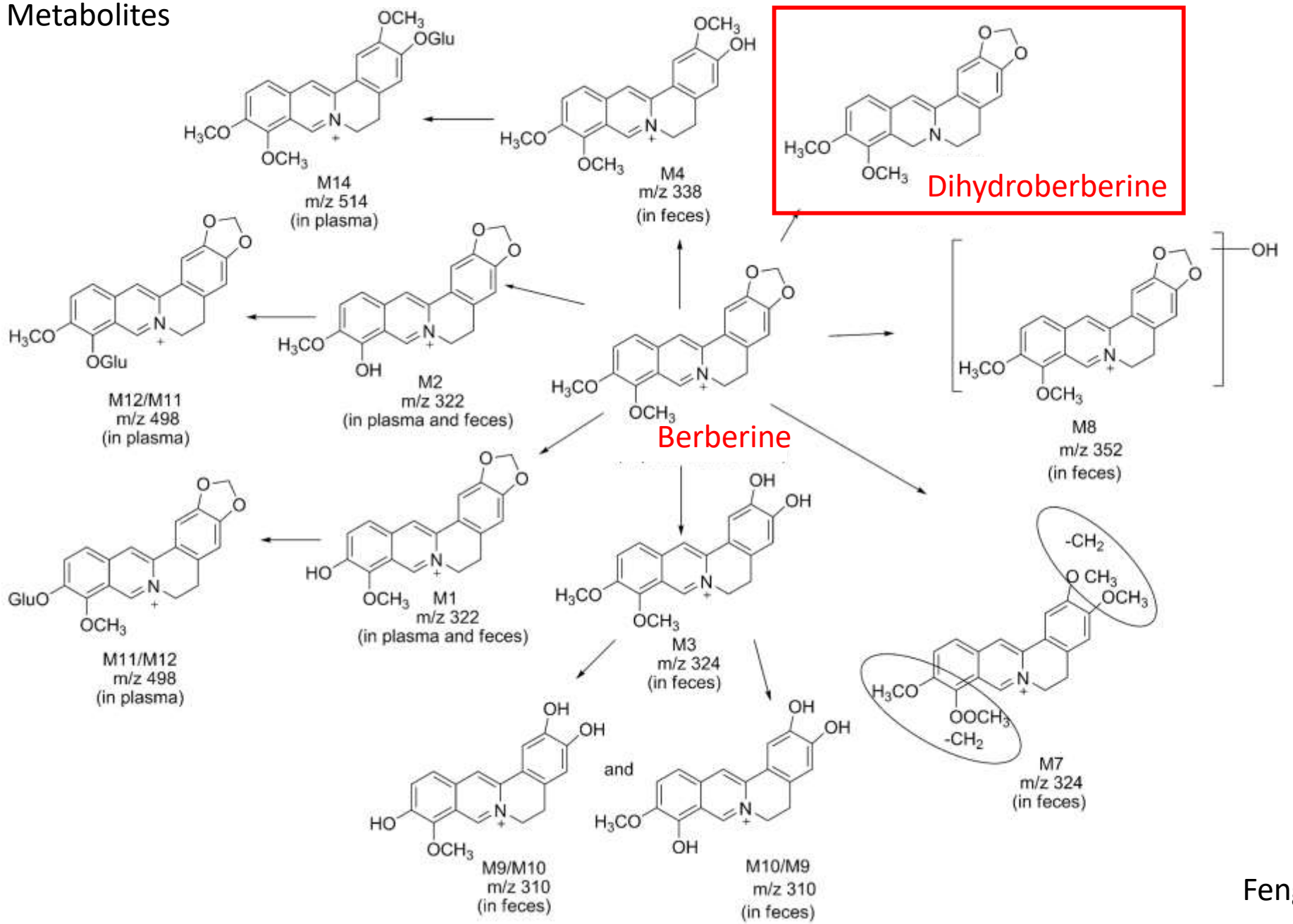
dhBBR
m/z 337

Dihydroberberine

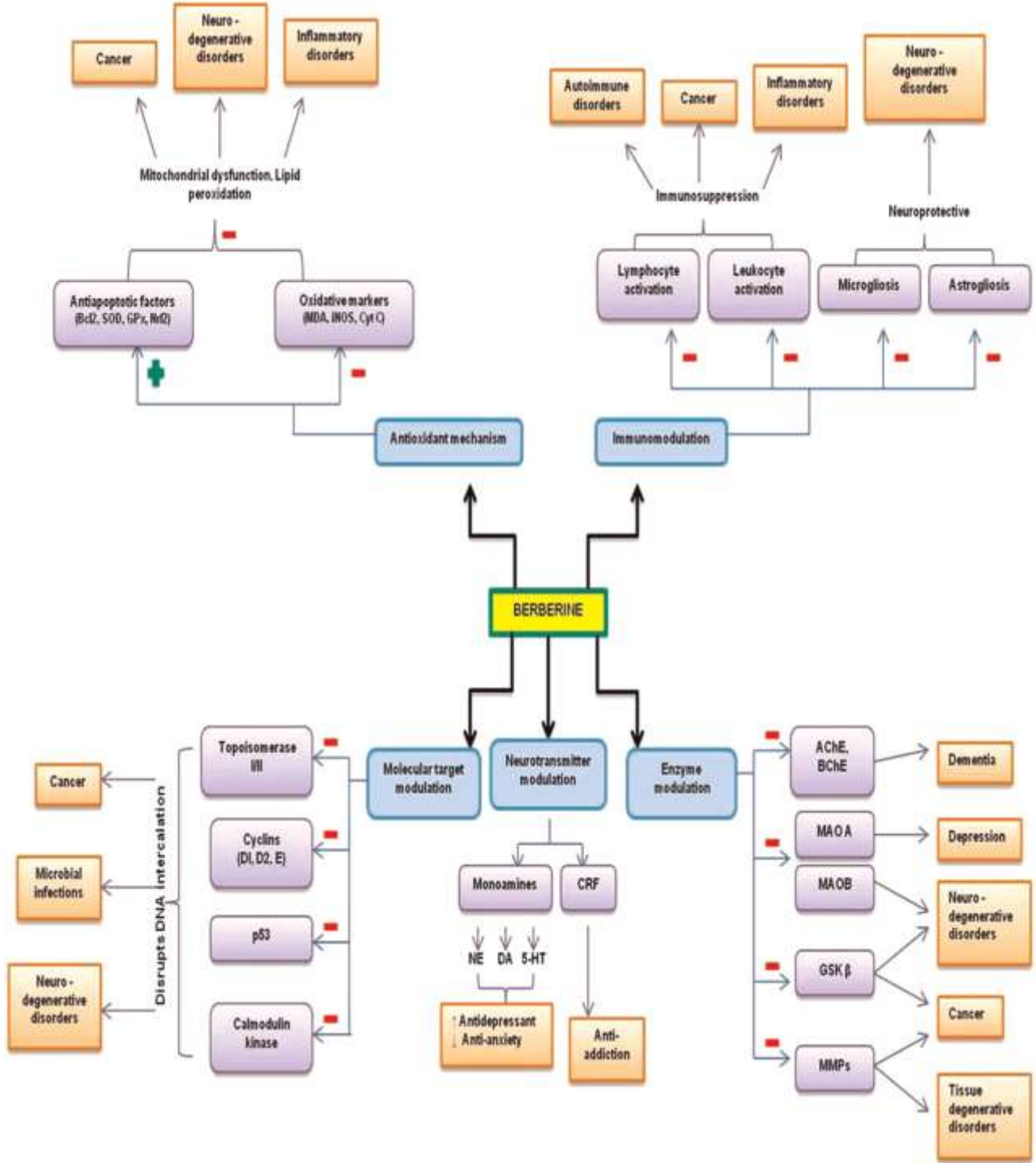


dhBBR
m/z 337

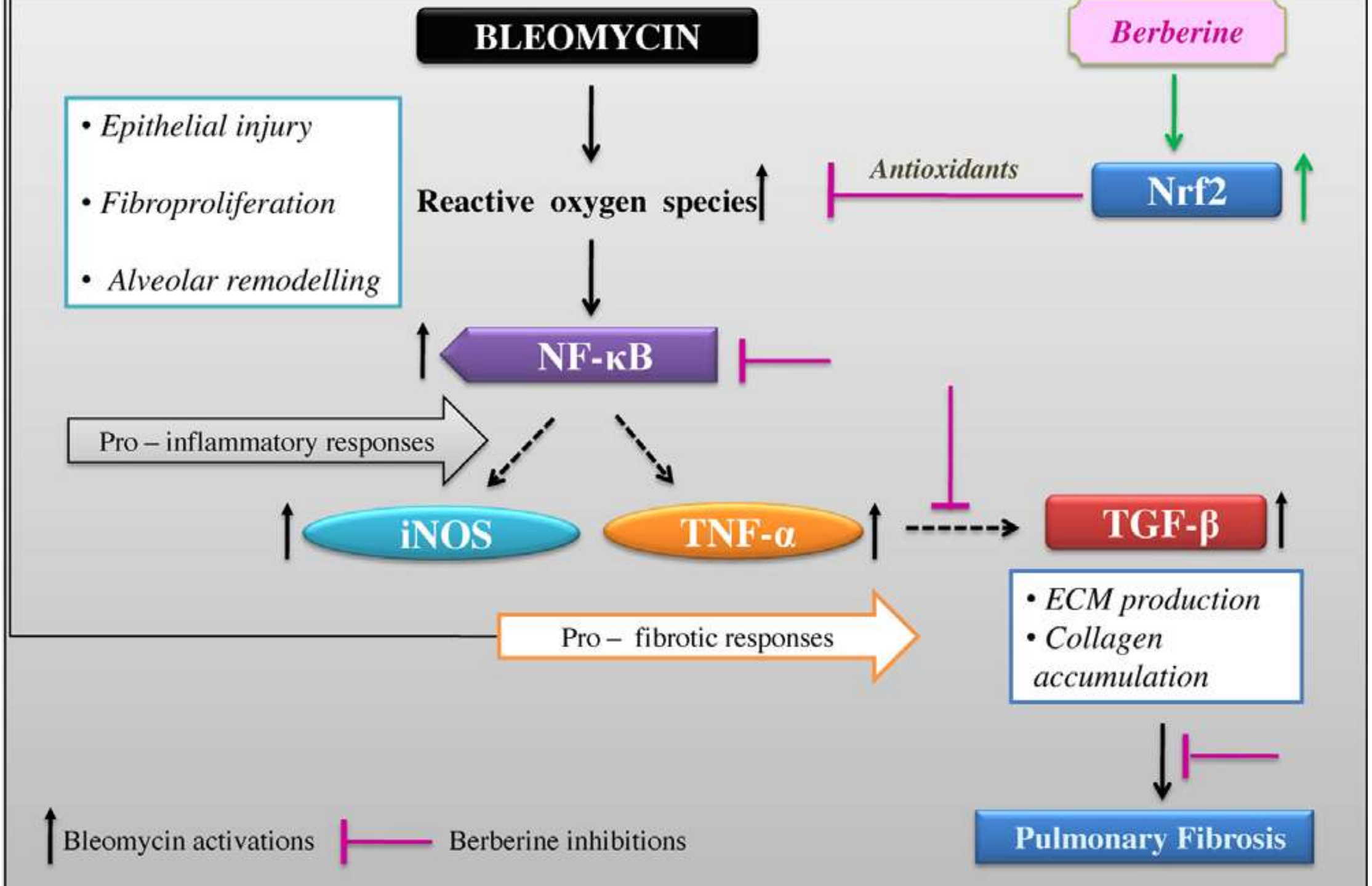
BERBERINE Metabolites



Feng et al. 2018

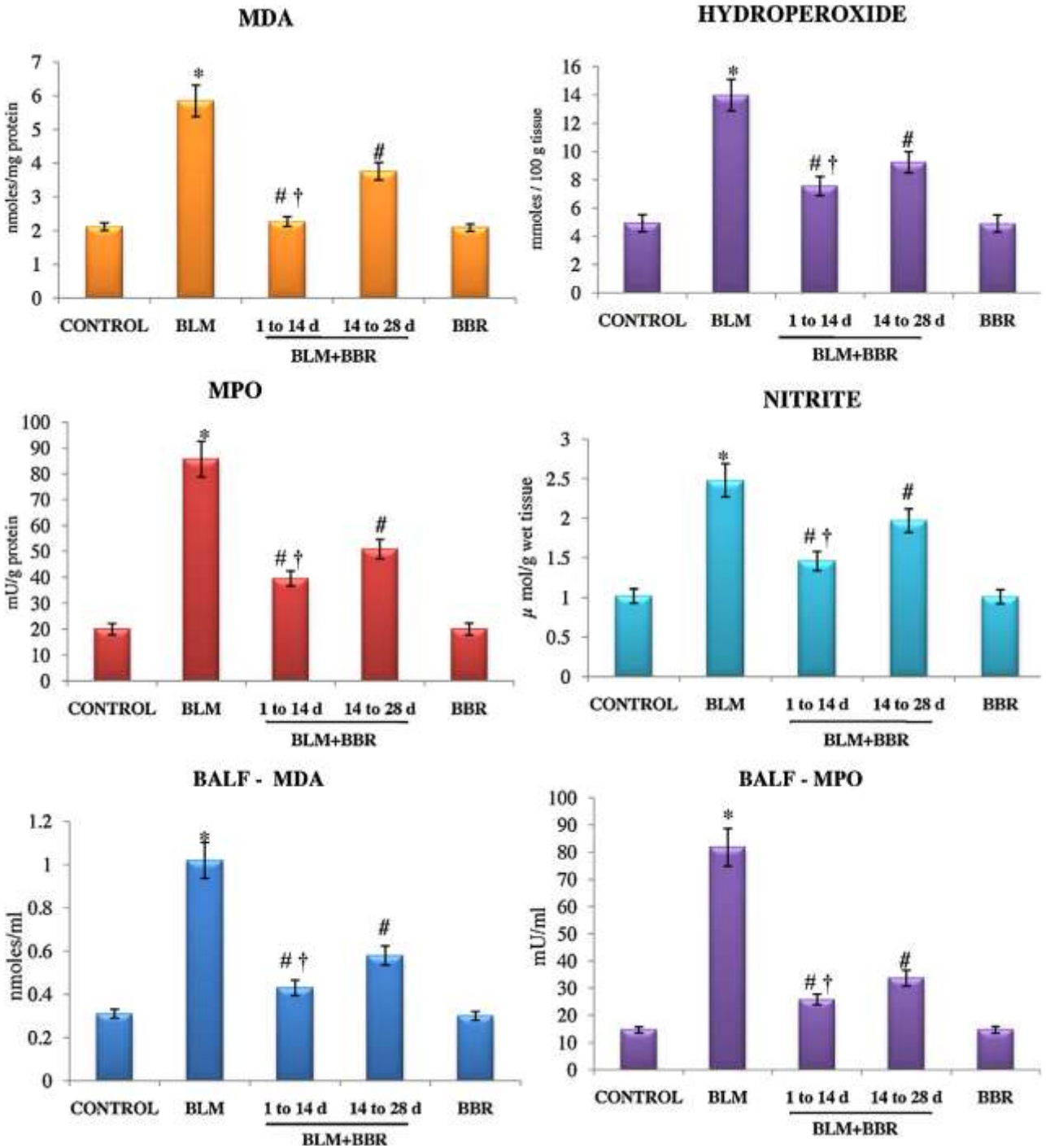


Kumar et al 2015

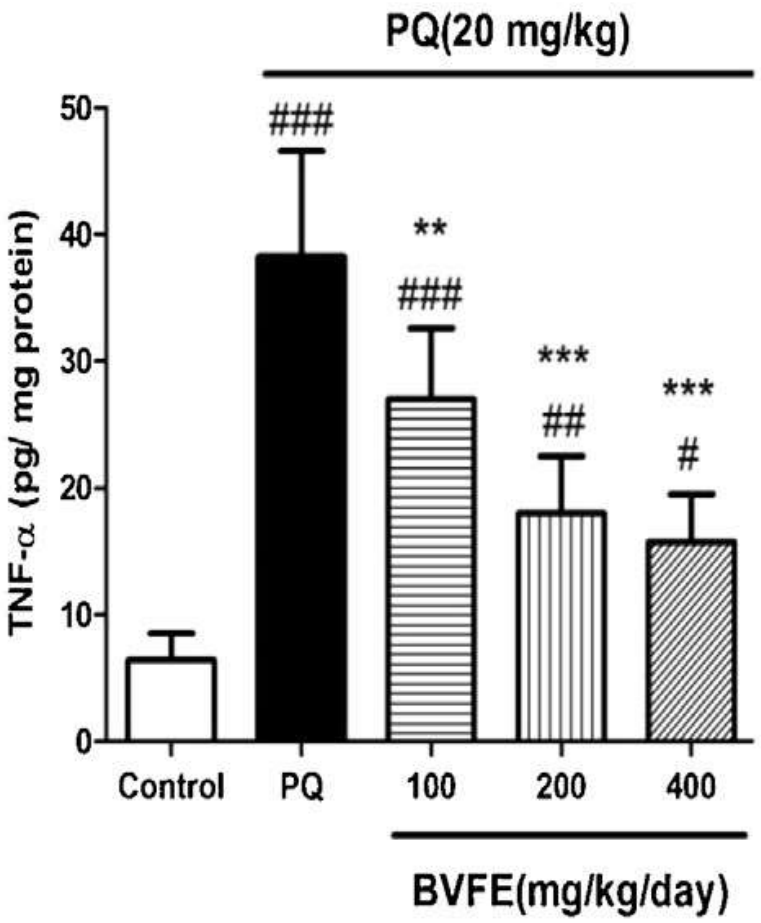

BLEOMYCIN
Berberine
• Epithelial injury
• Fibroproliferation
• Alveolar remodelling
Reactive oxygen species
Antioxidants
Nrf2
NF-κB
Pro – inflammatory responses
iNOS
TNF-α
TGF-β
• ECM production
• Collagen accumulation
Pro – fibrotic responses
Pulmonary Fibrosis
Bleomycin activations
Berberine inhibitions

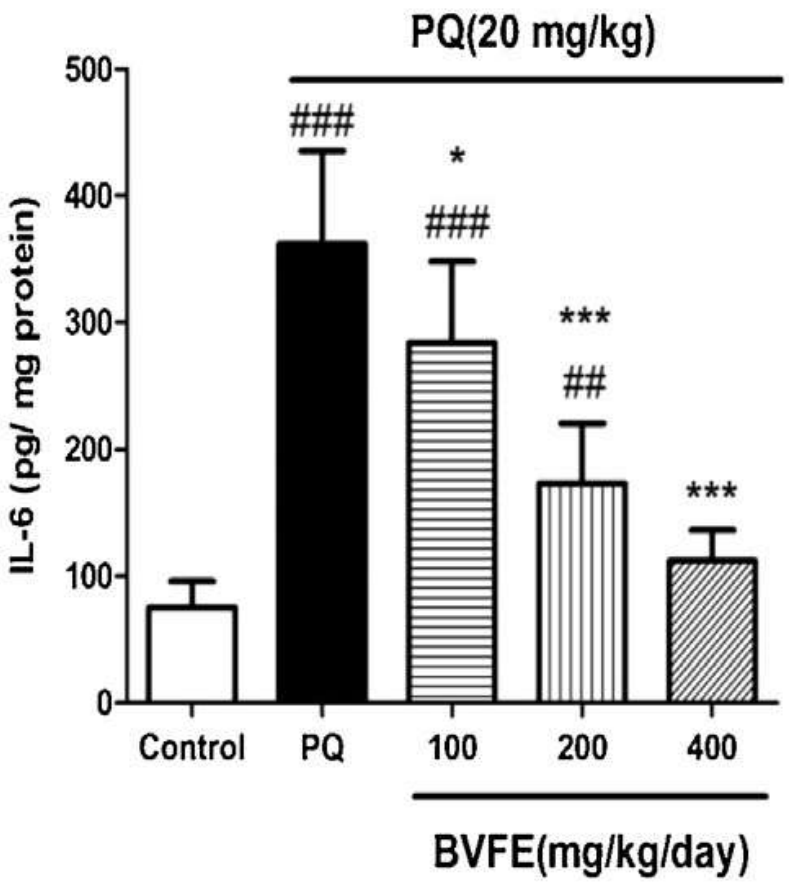
Control of Bleomycin induced pulmonary fibrosis in rats using Berberine (BBR)

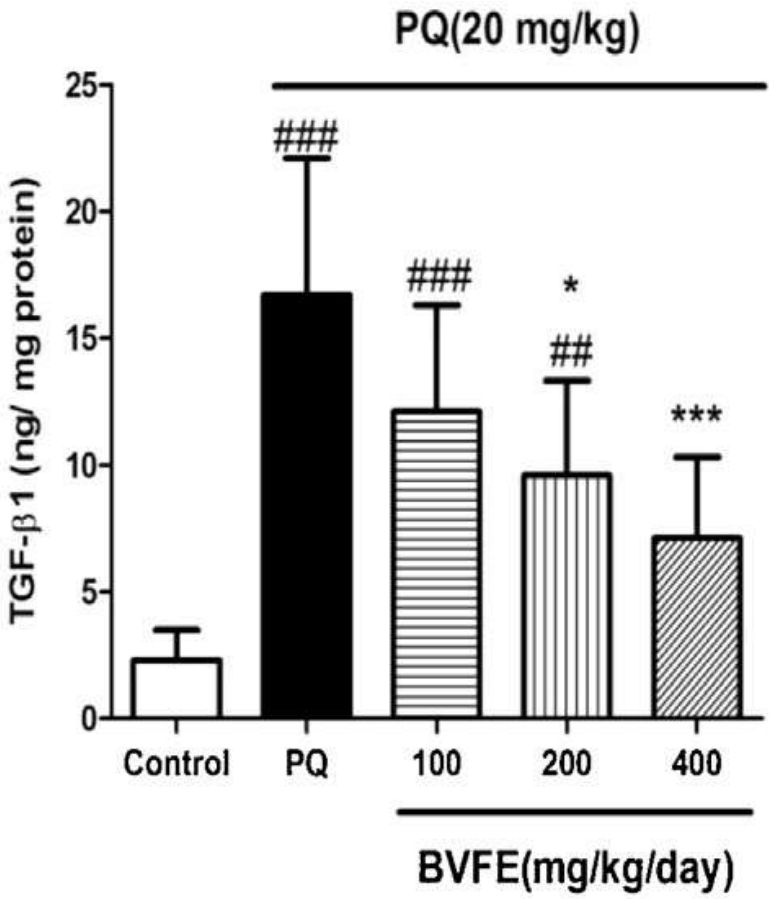
Chitra et al et al., 2013



Effect on paraquat (PQ) induced fibrosis in rats







BVFE – berberine delivered 1 wk before and during 3 wks of PQ
- p < 0.001 difference with control
*** - P < 0.001 difference with PQ dosed animals

Javad-Mousavi et al 2016

Interactions

Drug	Drug interaction	Inference	Reference
Tetrandine	P gp efflux of berberine is inhibited by tetrandine	Potentiation of hypoglycemic activity of berberine	Zhang et al. (2014)
L DOPA	Berberine leads to degeneration of dopaminergic neuronal cells in substantia nigra with chronic L DOPA administration	Antagonistic action	Shan et al. (2013)
Doxorubicin	Berberine sensitizes cells to anti cancer effects of doxorubicin	Synergistic effect	Shin et al. (2013)
β Lactam antibiotics	Berberine increases sensitivity of MRSA (methicillin resistant *Staphylococcus aureus*) to oxacillin, cefazolin and ampicillin	Synergistic effect	Tong et al. (2012)
Hydroxycamptothecine	Berberine and hydroxycamptothecine have synergistic anticancer effect on tumor cells by inhibiting topoisomerase	Synergistic effect	Lin and Wang (2011)
Panax ginseng	Berberine combined with total saponins of *Panax ginseng* decreases plasma brain natriuretic peptide (BNP), angiotensin II (Ang II) and norepinephrine levels	Improvement of heart function in CHF	Luo et al. (2011)
Cisplatin	Combined treatment with berberine results in loss of mitochondrial membrane potential, release in cytochrome c and caspase thereby resulting in apoptosis	Enhanced cytotoxic effect	Youn et al. (2008)
Fluconazole	Berberine enhances actvity against fluconazole resistant *Candida albicans*	Synergistic effect	Quan et al. (2006)
Cyclosporin A	Berberine elevates blood concentration of Cyclosporin A by inhitibiting CYP3A4	Reduction of Cyclosporin A	Wu et al. (2005)
Warfarin, thiopental	Berberine displaces warfarin and thiopental from their protein binding sites increasing their free levels in blood	Precipitation of toxicity	Tan et al. (2002)

QUESTIONS?